DESCRIPTION

MENIN-MLL INTERACTION INHIBITOR, PREPARATION METHOD THEREFOR AND USES THEREOF

TECHNICAL FIELD

The present invention relates to the technical field of chemical medicine, and in particular to a Menin-MLL interaction inhibitor, a preparation method therefor and uses thereof, in particular uses thereof in the treatment of tumors.

BACKGROUND ART

Mixed lineage leukemia (MLL) proteins are histone methyltransferases, which are crucial for epigenetic regulation of gene transcription. Many acute leukemias, including acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL) and mixed lineage leukemia (MLL), are featured with the presence of a chimeric MLL fusion protein resulting from the chromosomal translocation of a MLL gene located on chromosome 11 band q23 (11q23). The chimeric MLL fusion protein retains approximately 1,400 amino acids of the N-terminus of MLL, but is fused to one of approximately 80 chaperone proteins (for example, AF4, AF9, ENL, AF10, ELL, AF6, AF1p, and GAS7). The MLL fusion protein lacks the primitive histone methyltransferase activity at the C-terminus of MLL, and acquires the ability to regulate the transcription of numerous oncogenes (including HOX and MEIS1), resulting in increased cell proliferation and reduced cell differentiation, ultimately leading to leukemia.

Menin is a scaffold protein encoded by a multiple endocrine neoplasia type 1 (MEN1) gene. Menin mutations cause hereditary autosomal dominant neoplasia syndrome (MEN1 syndrome), resulting in the formation of tumors in several endocrine organs. The binding of Menin to the N-terminus of the MLL fusion protein is necessary for the observed oncogenic activity of the MLL fusion protein. This binding has been shown to constitutively upregulate the expression of HOX and MEIS1 oncogenes and to impair the proliferation and differentiation of hematopoietic cells, resulting in leukemia. MLL1 acts as a universal transcriptional activator for various gene regulatory pathways. In MLL fusion leukemias featured with distinct chromosomal translocations at 11q23, Menin is critical for maintaining MLL-associated myeloid transformation. In gene knockdown experiments, when the function of Menin decreases, the abnormal gene expression program mediated by MLL fusion is abolished. Furthermore, other studies have described the importance of Menin-MLL interaction in breast cancer, prostate cancer, synovial sarcoma and hepatocellular carcinoma. In these indications, the interactions between Menin and MLL fusion proteins and between Menin and MLL have been described to strictly regulate the expression of disease-related genes. Inhibiting the binding of Menin to MLL has recently become a new therapeutic strategy. Its beneficial therapeutic effects have been assumed in the models of leukemia, prostate cancer, breast cancer, colon cancer, liver cancer and synovial sarcoma. Hence, the interactions between Menin and MLL fusion proteins and between Menin and MLL represent potential small molecule therapeutic targets.

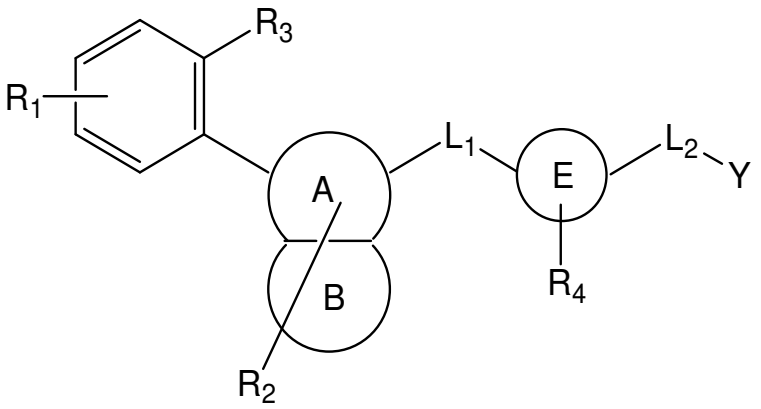
The nucleophosmin 1 (NPM1) gene encodes for a multifunctional protein located primarily in the nucleolus. Mutations in the NPM1 gene lead to its aberrant cytoplasmic localization (NPM1c). The interaction between MLL and Menin in NPM1-mutated AML shares common HOX gene characteristics and dependence with the rearrangement of MLL and Menin. AML cells with NPM1 mutations rely on the interaction between Menin and wild-type MLL to maintain this leukemogenesis, and these cells are sensitive to the blockade of Menin-MLL binding. Both MLL gene rearrangements and NPM1c can be targeted in the same manner, since MLL fusion proteins and wild-type MLL share a common amino-terminal domain.

The rearrangement of MLL genes occur in 5-10% of acute leukemia cases, and are particularly common in infantile acute leukemias (up to 70% of cases). MLL gene-rearranged leukemic subtypes are characterized by invasiveness, treatment resistance and high rates of early recurrence, even after initial complete remission. Leukemia patients, especially infants, with MLL gene chromosomal translocations have a very poor prognosis, with a 5-year survival rate of less than 40%. NPM1 is the most commonly mutant gene (approximately 30%) in adult acute myeloid leukemia (AML). There is an urgent need for a novel therapeutic strategy to treat this leukemia. Therefore, a small molecule inhibitor that blocks the Menin-MLL interaction represents a valuable target for the treatment of diseases involving MLL fusion proteins, exhibiting great importance in providing new options for cancer treatment.

SUMMARY OF THE INVENTION

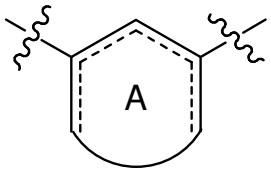
In view of the need in the prior art, the present invention provides a Menin-MLL interaction inhibitor, a preparation method therefor and uses thereof.

In a first aspect of the present invention, there is provided a compound or a pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, wherein the compound has a structure of:



(I),

wherein,



Ring A is , ------ represents a single or double bond, and said Ring A is a five- to seven-membered aromatic or heterocyclic ring;

Ring B is a five- to seven-membered nitrogenous heterocyclic ring;

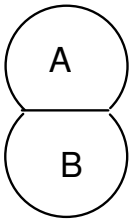
Ring E is a three- to eight-membered saturated or partially saturated aliphatic ring, an aromatic ring, or a four- to twelve-membered saturated or partially saturated heterocyclic ring;

L_1 and L_2 are independently selected from the group consisting of: a single bond, C_1-C_{10} alkylene, and -(C_0-C_{10} alkylene)-Q-(C_0-C_{10} alkylene)- , with Q selected from the group consisting of: -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{La})-, -N(R_{La})C(O)-, -N(R_{La})C(O)O-, -N(R_{La})C(O)N(R_{La})-, -N(R_{La})-, -S(O)$_2$-, -S(O)$_2$N(R_{La})-, -N(R_{La})S(O)$_2$-, -S(O)-, -S(O)N(R_{La})-, -N(R_{La})S(O)-, -C(=NR_{La})-, and -C(=NR_{La})-NR_{La}-; H atom(s) in said alkylene can be optionally substituted with a group selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4-10-membered heterocyclyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, hydroxyl, C_1-C_{10} alkoxy, halogenated C_1-C_{10} alkoxy, amino, and C_1-C_{10} alkylamino; H in said cycloalkyl, aryl or heterocyclyl may be optionally substituted with a group selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, and halogenated C_1-C_{10} alkyl; R_{La} is selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl;

R_1 is one or more independent substituents on the benzene ring, and each R_1 is independently selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{101}, -C(O)R_{101}, -C(O)OR_{101}, -NR_{102}C(O)OR_{101}, -OC(O)R_{101}, -NR_{102}SO_2R_{101}, -SO_2N$R_{101}R_{102}$, -NR_{102}C(O)R_{101}, -C(O)N$R_{101}R_{102}$, -N$R_{101}R_{102}$, -SR_{101}, -S(O)R_{101}, -SO_2R_{101}, -SO_3H, -NR_{102}(C$R_{103}R_{104}$)$_t$OR_{101}, -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with t being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -

NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_{101} to R_{104} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;



R_2 is one or more independent substituents on a ring, and each R_2 is independently selected from the group consisting of: H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{201}, -$C(O)R_{201}$, -$C(O)OR_{201}$, -$NR_{202}C(O)OR_{201}$, -$OC(O)R_{201}$, -$NR_{202}SO_2R_{201}$, -$SO_2NR_{201}R_{202}$, -$NR_{202}C(O)R_{201}$, -$C(O)NR_{201}R_{202}$, -$NR_{201}R_{202}$, -SR_{201}, -$S(O)R_{201}$, -$S(O)_2R_{201}$, -SO_3H, -$NR_{202}(CR_{203}R_{204})_jOR_{201}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with j being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_{201} to R_{204} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_3 is selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{301}, -$C(O)R_{301}$, -$C(O)OR_{301}$, -$NR_{302}C(O)OR_{301}$, -$OC(O)R_{301}$, -$NR_{302}SO_2R_{301}$, -$SO_2NR_{301}R_{302}$, -$NR_{302}C(O)R_{301}$, -$C(O)NR_{301}R_{302}$, -$NR_{301}R_{302}$, -SR_{301}, -$S(O)R_{301}$, -$S(O)_2R_{301}$, -SO_3H, -$NR_{302}(CR_{303}R_{304})_iOR_{301}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with i being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

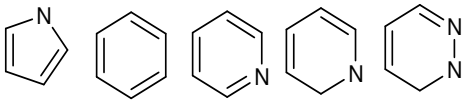
R_{301} to R_{304} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -

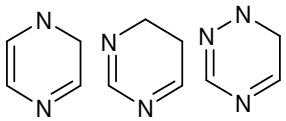
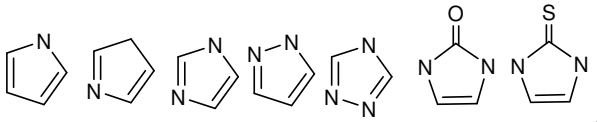
$SO_2NR'R''$, $-NR'C(O)R''$, $-C(O)NR'R''$, $-NR'R''$, $-SR'$, $-SOR'$, $-SO_2R'$, $-SO_3H$, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;
or, R_{301} and R_{302}, together with the atom attached thereto, form heterocyclyl, and said heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, $-OR_5$, $-C(O)R_5$, $-C(O)OR_5$, $-NR_6C(O)OR_5$, $-OC(O)R_5$, $-NR_6SO_2R_5$, $-SO_2NR_5R_6$, $-NR_6C(O)R_5$, $-C(O)NR_5R_6$, $-NR_5R_6$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-SO_3H$, -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), $-SO_2$-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), $-SO_2$-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), $-SO_2$-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl); wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', $-NR'C(O)OR''$, $-NR'SO_2R''$, $-SO_2NR'R''$, $-NR'C(O)R''$, $-C(O)NR'R''$, $-NR'R''$, -SR', -SOR', $-SO_2R'$, $-SO_3H$, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;
R_5 and R_6 are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', $-NR'C(O)OR''$, $-NR'SO_2R''$, $-SO_2NR'R''$, $-NR'C(O)R''$, $-C(O)NR'R''$, $-NR'R''$, -SR', -SOR', $-SO_2R'$, $-SO_3H$, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;
R_4 is one or more independent substituents on Ring E, and each R_4 is independently selected from the group consisting of: H, halogen, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, $-OR_{401}$, $-C(O)R_{401}$, $-C(O)OR_{401}$, $-NR_{102}C(O)OR_{401}$, $-OC(O)R_{401}$, $-NR_{402}SO_2R_{401}$, $-SO_2NR_{401}R_{402}$, $-NR_{402}C(O)R_{401}$, $-C(O)NR_{401}R_{402}$, $-NR_{401}R_{402}$, $-SR_{401}$, $-S(O)R_{401}$, $-S(O)_2R_{401}$, $-SO_3H$, $-NR_{402}(CR_{403}R_{404})_mOR_{104}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), $-SO_2$-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), $-SO_2$-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), $-SO_2$-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with m being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', $-NR'C(O)OR''$, $-NR'SO_2R''$, $-SO_2NR'R''$, $-NR'C(O)R''$, $-C(O)NR'R''$, $-NR'R''$, -SR', -SOR', $-SO_2R'$, $-SO_3H$, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;
R_{401} to R_{404} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', $-NR'C(O)OR''$, $-NR'SO_2R''$, $-SO_2NR'R''$, $-NR'C(O)R''$, $-C(O)NR'R''$, $-NR'R''$, -SR', -SOR', $-SO_2R'$, $-SO_3H$, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;
Y is selected from the group consisting of: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, three- to eight-membered saturated or partially saturated alcyl, aryl, four- to twelve-membered heterocyclyl, aryl-fused three- to eight-membered alcyl, aryl-fused three- to eight-membered heterocyclyl, three- to eight-membered aliphatic ring-fused aryl, three- to eight-membered aliphatic ring-fused heterocyclyl, three- to eight-membered heterocyclic ring-fused three- to eight-membered aliphatic ring, three- to eight-membered heterocyclic ring-fused aryl, and three- to eight-membered heterocyclic ring-fused five- to ten-membered heterocyclyl, and Y may be optionally substituted with one or more R^Y groups, with R^Y selected from the group consisting of: H, =O, , C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-NR_8C(O)OR_7$, $-OC(O)R_7$, $-NR_8SO_2R_7$, $-SO_2NR_7R_8$, $-NR_7C(O)R_8$, $-C(O)NR_7R_8$, $-NR_7R_8$, $-SR_7$, $-S(O)R_7$, $-S(O)_2R_7$, $-SO_3H$, -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), $-SO_2$-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), $-SO_2$-

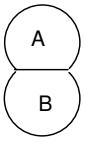
(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl); wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

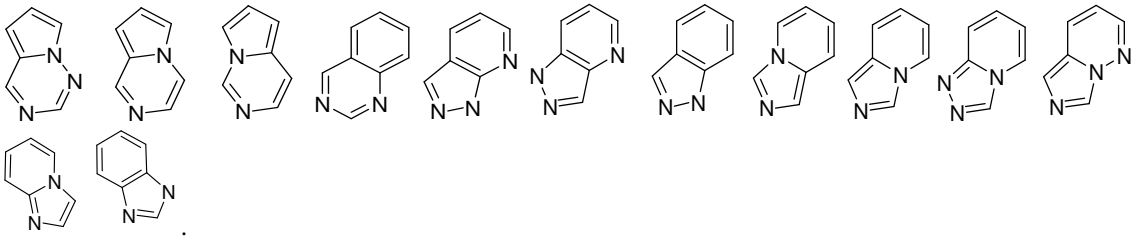
R_7 and R_8 are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl alkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclyl alkyl; wherein the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

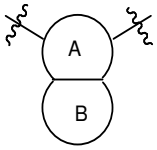
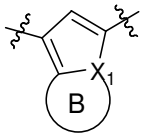
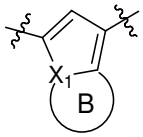
R' and R" are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl.

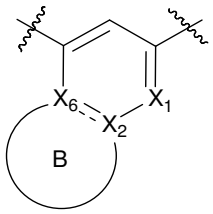
In some embodiments of the present invention, Ring A is a five- or six-membered aromatic or nitrogenous heterocyclic aromatic ring, for example,  .

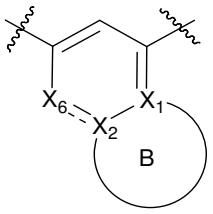
In some embodiments of the present invention, Ring B is a five-membered or six-membered nitrogenous heterocyclic ring, for example,  or  .

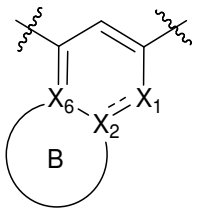
In some embodiments of the present invention, Ring  is one of the following structures:

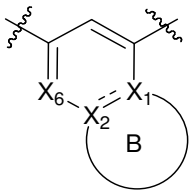
 .

In some embodiments of the present invention, the  moiety is  ,  ,

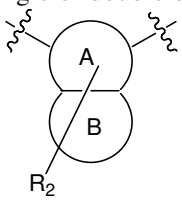


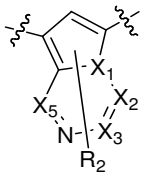


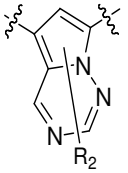


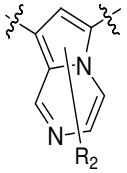


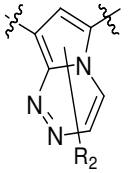
, , , or , wherein X_1 is N or C, X_2 is N or C, X_6 is N or C, and ------ represents a single or double bond.

In some embodiments of the present invention, the 

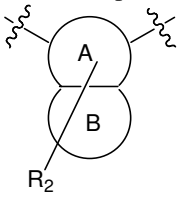
moiety is 

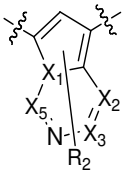
, wherein X_1 is N or C, X_2 is N or C, X_3 is N or C, and X_5 is N or C, for example, 

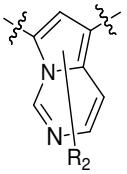
, 

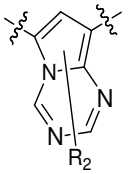
, or 

.

In some embodiments of the present invention, the 

moiety is 

, wherein X_1 is N or C, X_2 is N or C, X_3 is N or C, and X_5 is N or C, for example, 

, or 

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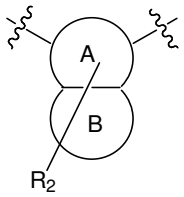
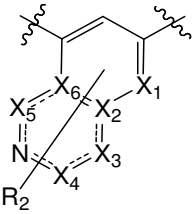
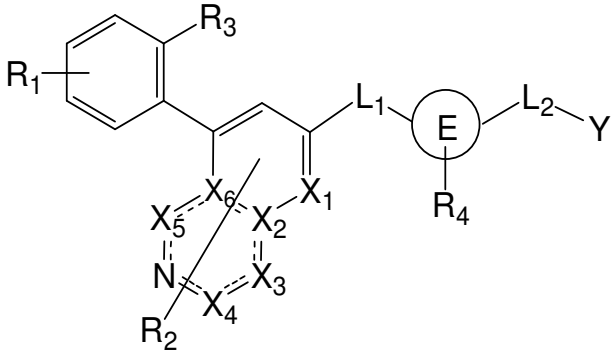
In some embodiments of the present invention, the 

moiety is 

, wherein X_1 is N or C, X_2 is N or C, X_3 is N or C, X_4 is N or C or absent (that is, X_3 is directly linked to N), X_5 is N or C or absent (that is, X_6 is directly linked to N), X_6 is N or C, and ------ represents a single or double bond. In some embodiments of the present invention, the compound has a structure as follows:

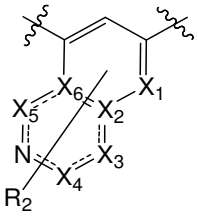
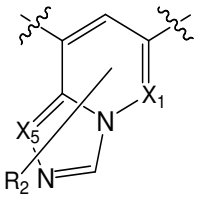
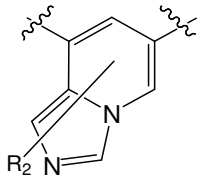
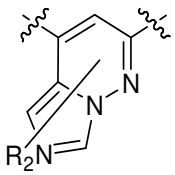
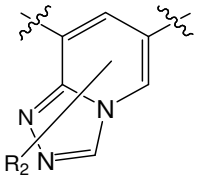
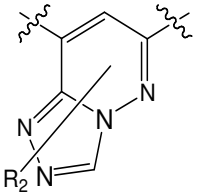


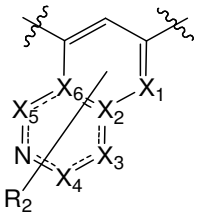
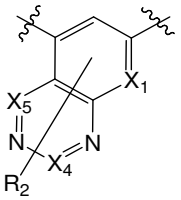
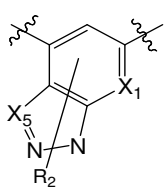
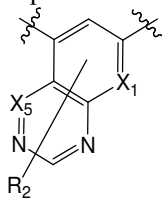
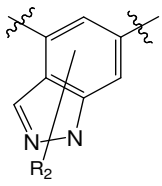
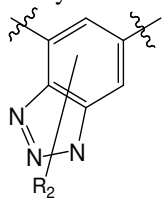
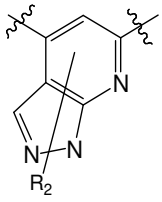
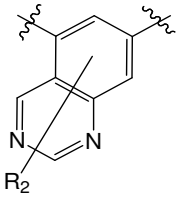
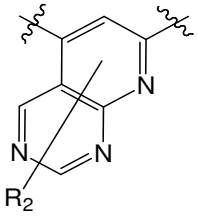
(II).

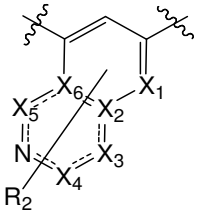
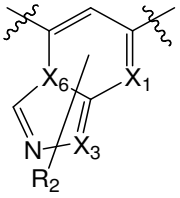
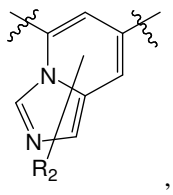
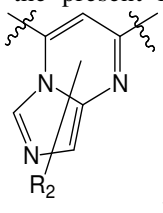
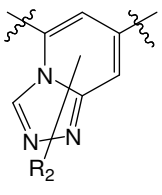
In some embodiments of the present invention, X_2 is N.

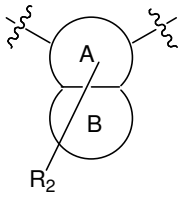
In some embodiments of the present invention, X_3 is absent.

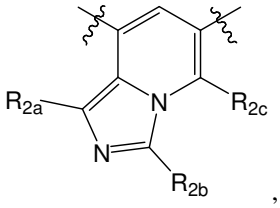
In some embodiments of the present invention, X_4 is C.

In some embodiments of the present invention, the  moiety is  , for example,  ,  ,  or  .

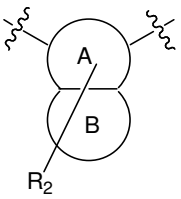
In some embodiments of the present invention, the  moiety is  , for example,  or  , for example,  ,  ,  ,  , or  .

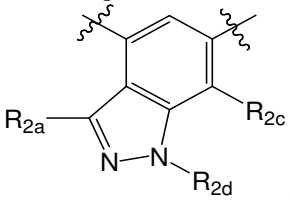
In some embodiments of the present invention, the  moiety is  , for example,  ,  , or  .

In a preferred embodiment of the present invention, the 

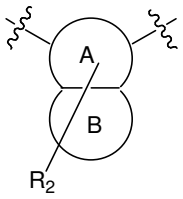
moiety is 

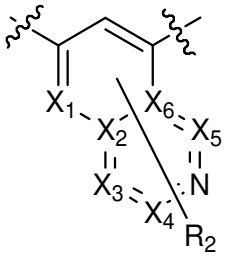
, wherein R_{2a}, R_{2b}, or R_{2c} is defined as those defined for R_2 above.

In a preferred embodiment of the present invention, the 

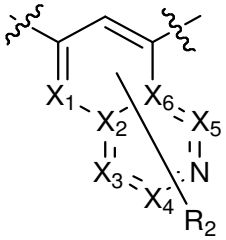
moiety is 

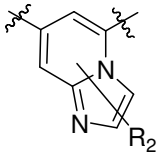
, wherein R_{2a}, R_{2d}, or R_{2c} is defined as those defined for R_2 above.

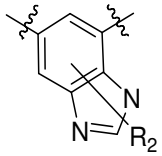
In some embodiments of the present invention, the 

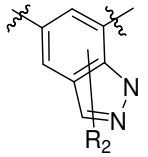
moiety is 

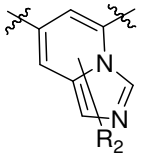
, wherein X_1 is N or C, X_2 is N or C, X_3 is N or C, X_4 is N or C or absent (that is, X_3 is directly linked to N), X_5 is N or C or absent (that is, X_6 is directly linked to N), X_6 is N or C, and ------ represents a single or double bond.

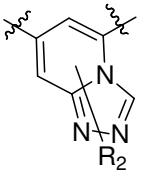
In some embodiments of the present invention, the 

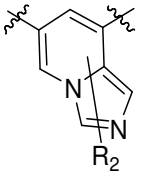
moiety is for example 

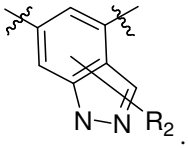
, 

, 

, 

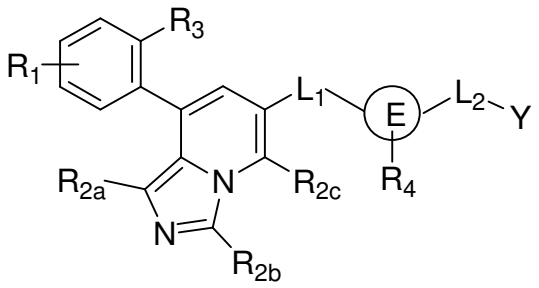
, 

, 

, or 

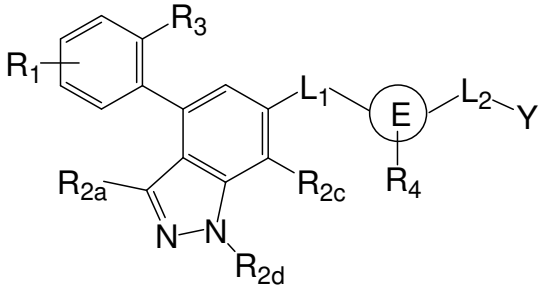
.

In some embodiments of the present invention, the compound has a structure as follows:

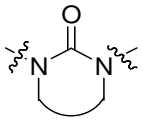
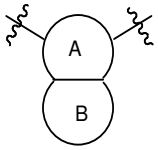
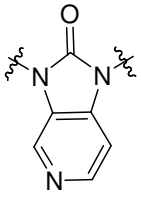


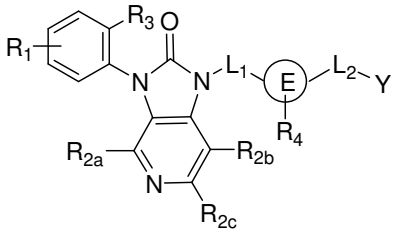
(III).

In some embodiments of the present invention, the compound has a structure as follows:

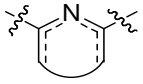
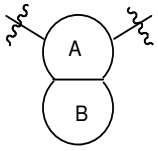


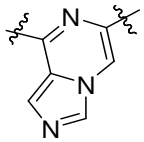
(IV).

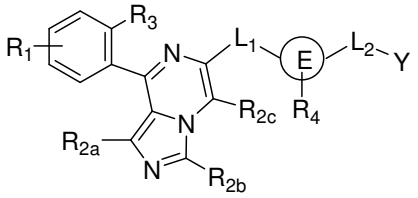
In other embodiments of the present invention, Ring A is  , and Ring B is an aromatic ring or a five- or six-membered nitrogenous heterocyclic aromatic ring, for example, the  moiety may be  . In some embodiments of the present invention, the compound has a structure as follows:



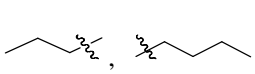
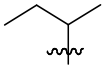
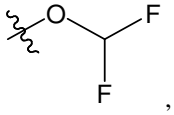
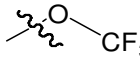
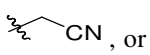
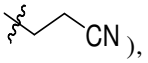
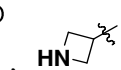
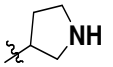
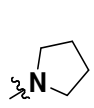
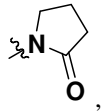
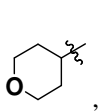
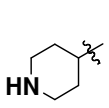
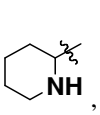
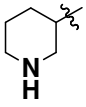
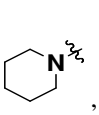
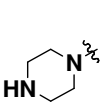
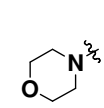
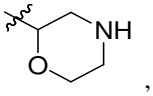
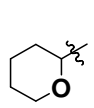
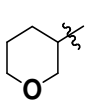
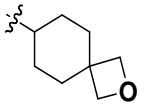
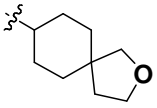
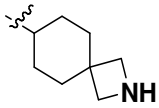
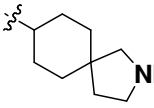
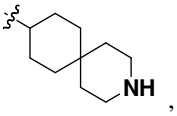
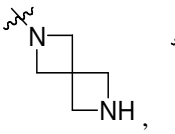
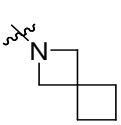
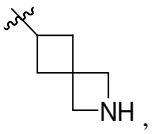
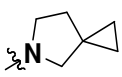
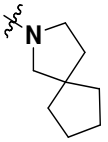
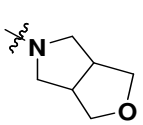
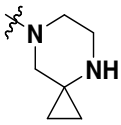
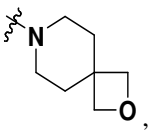
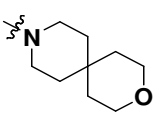
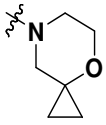
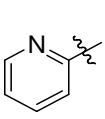
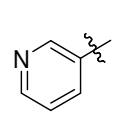
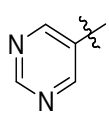
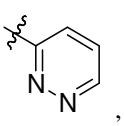
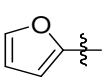
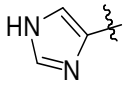
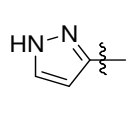
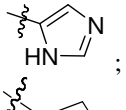
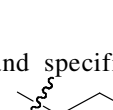
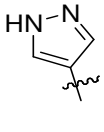
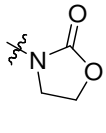
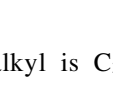
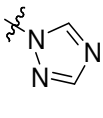
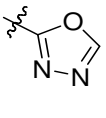
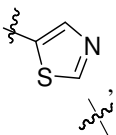
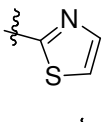
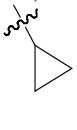
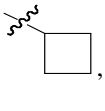
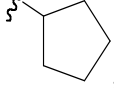
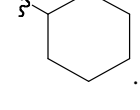
.

In other embodiments of the present invention, Ring A is  , and Ring B is an aromatic ring or a five- or six-membered nitrogenous heterocyclic aromatic ring, for example, the  moiety may

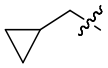
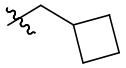
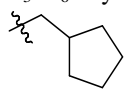
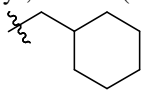
be  .In some embodiments of the present invention, the compound has a structure as follows:



.

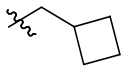
In some embodiments of the present invention, R_2 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, -CH_3, , ,  , or ), halogen (for example, F or Cl), cyano, nitro, azido, halogenated C_1-C_6 alkyl (for example, -CHF_2, -CH_2F, -CF_3, -CH_2-CH_2F, -CH_2-CHF_2, -CH_2-CF_3, -CH_2CH_2-CF_3, or -$CH_2CH_2CH_2$-CF_3), halogenated C_1-C_6 alkoxy (for example,  , or ), C_1-C_6 cyanoalkyl (for example,  , or ), -OR_{201}, -$C(O)R_{201}$, -$C(O)OR_{201}$, -$NR_{202}C(O)OR_{201}$, -$OC(O)R_{201}$, -$NR_{202}SO_2R_{201}$, -$SO_2NR_{201}R_{202}$, -$NR_{202}C(O)R_{201}$, -$C(O)NR_{201}R_{202}$, -$NR_{201}R_{202}$, -SR_{201}, -$S(O)_2R_{201}$, -SO_3H, -(C_0-C_3 alkylene)-(phenyl), -(C_0-C_3 alkylene)-(4-10-membered heterocyclyl), and -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl); wherein the phenyl, 4-10-membered heterocyclyl, or C_3-C_{10} cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_3 alkyl, and C_1-C_3 halogenated alkyl. Specifically, the 4-10-membered heterocyclic ring is a 4-6-membered heterocyclic ring , for example, ,  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or  ; and specifically, the C_3-C_8 cycloalkyl is C_3-C_6 cycloalkyl, for example, ,  ,  ,  , or .

In some embodiments of the present invention, R_{201} is selected from H and C_{1-6} alkyl.

In some embodiments of the present invention, R_{202} is selected from the group consisting of: H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and -(C_1-C_3 alkylene)-(C_3-C_6 cycloalkyl) (for example,  ,  ,  , or ).

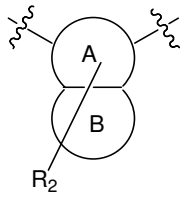
In some embodiments of the present invention, R_2 is selected from the group consisting of: H, C_1-C_6 alkyl, halogen, cyano, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, -O(C_0-C_6 alkyl), -C(O)(C_0-C_6 alkyl), and -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl).

In some embodiments of the present invention, R_{2a} is selected from the group consisting of: H and halogen (for example, F or Cl).

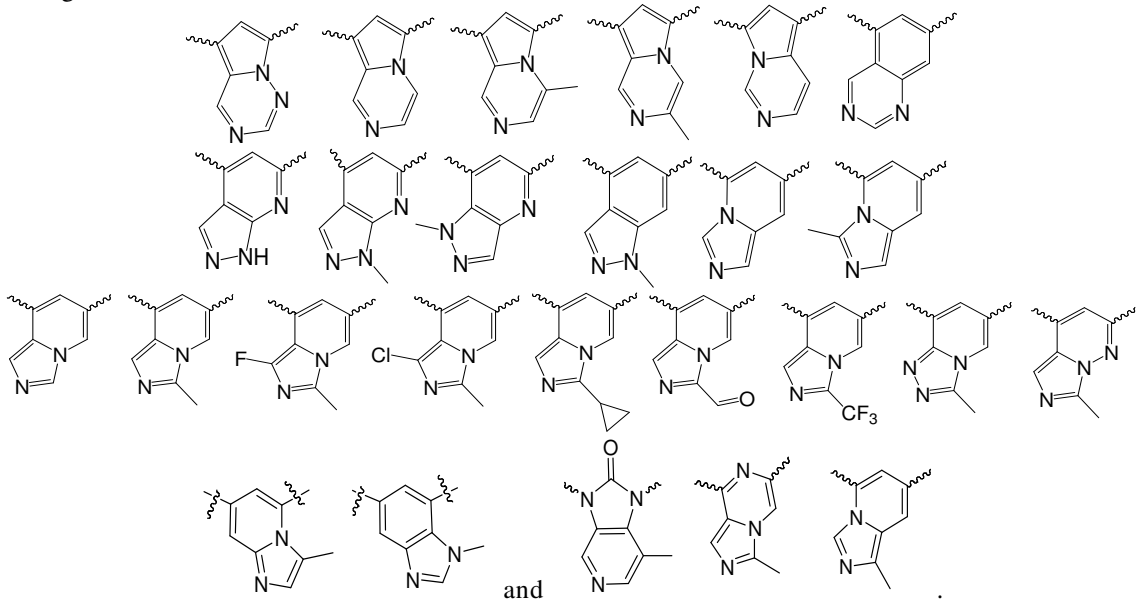
In some embodiments of the present invention, R_{2b} is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl), halogenated C_1-C_6 alkyl (for example, -CF_3), halogenated C_1-C_6 alkoxy (for example, -OCF_3), -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl) (for example, , , , or ), and -C(O)(C_0-C_6 alkyl) (for example,).

In some embodiments of the present invention, R_{2c} is selected from the group consisting of: H and halogen (for example, F or Cl).

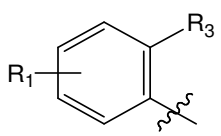
In some embodiments of the present invention, R_{2d} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), and -C(O)(C_0-C_6 alkyl), in particular H or C_1-C_3 alkyl (for example, methyl).

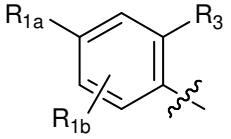
In some embodiments of the present invention, the 

moiety is selected from the group consisting of:



and .

In some embodiments of the present invention, the 

moiety is 

,

wherein R_{1a} is H or halogen (for example, F or Cl), and R_{1b} is one or more independent substituents on a benzene ring, and is defined as those defined for R_1 above.

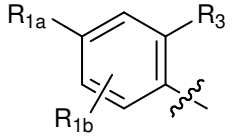
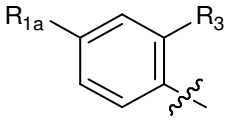
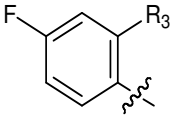
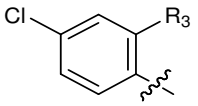
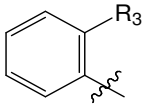
Specifically, R_1 may be independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, halogen, cyano, nitro, azido, halogenated C_1-C_6 alkyl, -N(C_0-C_6 alkyl)C(O)(C_0-C_6 alkyl), and -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl).

In some embodiments of the present invention, R_{1a} is H.

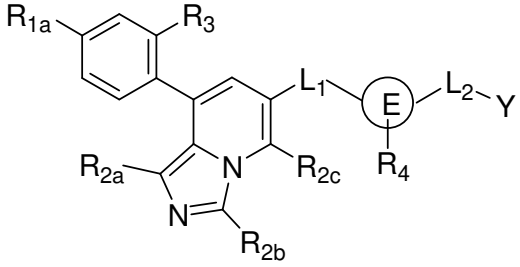
In some embodiments of the present invention, R_{1a} is F.

In some embodiments of the present invention, R_{1a} is Cl.

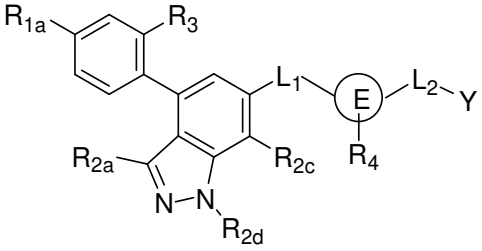
In some embodiments of the present invention, R_{1b} is H.

More specifically, the  moiety may be  , for example,  ,  , or  .

In some embodiments of the present invention, the compound has a structure as follows:



(V-1)



(V-2).

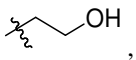
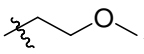
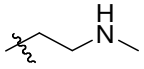
In some embodiments of the present invention, R_3 is -$NR_{302}C(O)R_{301}$ or -$C(O)NR_{301}R_{302}$.

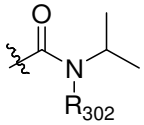
In some embodiments of the present invention, R_{301} or R_{302} is independently selected from the group consisting of: H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_3-C_{10} cycloalkylalkyl, optionally substituted 4-10-membered heterocyclyl, optionally substituted 4-10-membered heterocyclylalkyl; or, R_{301} and R_{302}, together with the atom attached thereto, form optionally substituted 4-8-membered saturated or partially saturated heterocyclic ring (in particular, saturated heterocyclic ring).

In some embodiments of the present invention, R_{301} or R_{302} is independently selected from the group consisting of: H, C_1-C_6 alkyl, -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), and -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl, and R' and R'' are each independently selected from the group consisting of: H and C_1-C_6 alkyl.

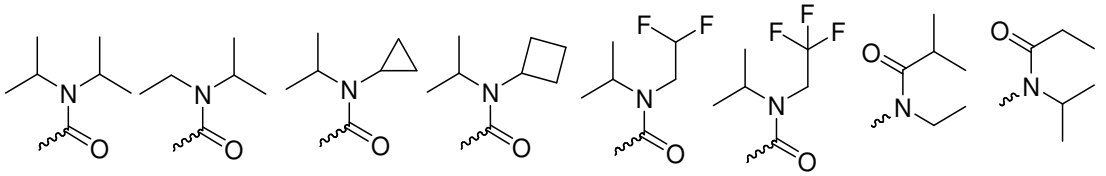
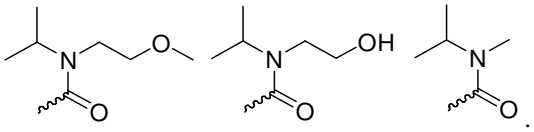
In some embodiments of the present invention, R_{301} or R_{302} is independently selected from the group consisting of: H, C_1-C_6 alkyl (in particular, ethyl, or isopropyl), C_3-C_6 cycloalkyl (for example, cyclopropyl, or cyclobutyl), -(C_1-C_3 alkylene)-(C_3-C_6 cycloalkyl), halogenated C_1-C_6 alkyl (for example, -CHF_2, -CF_3, -CH_2-CHF_2, or -CH_2-CF_3), -(C_1-C_3 alkylene)-O-(C_0-C_3 alkyl), and -(C_1-C_3 alkylene)-NH-(C_0-C_3 alkyl).

In some embodiments of the present invention, R_{301} is isopropyl.

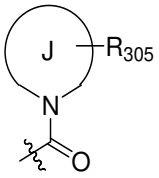
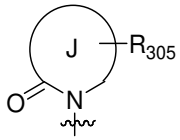
In some embodiments of the present invention, R_{302} is selected from the group consisting of: H, C_1-C_6 alkyl (for example, ethyl, or isopropyl), halogenated C_1-C_6 alkyl (for example, -CH_2-CHF_2, or -CH_2-CF_3), C_3-C_6 cycloalkyl (for example, cyclopropyl, or cyclobutyl), -(C_1-C_3 alkylene)-O-(C_0-C_3 alkyl) (for example,  , or ), and -(C_1-C_3 alkylene)-NH-(C_0-C_3 alkyl) (for example, ).

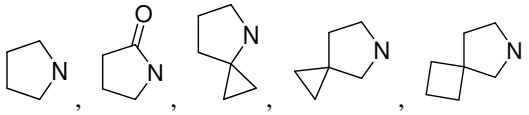
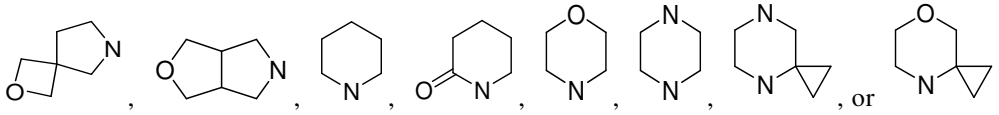
In some embodiments of the present invention, R_3 is  .

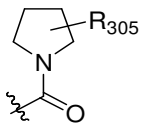
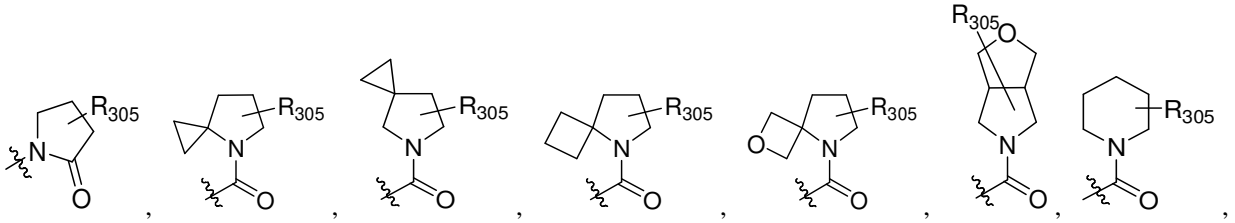
In some embodiments of the present invention, R_3 is selected from the group consisting of:

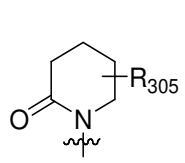
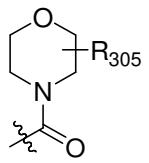
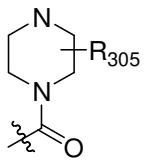
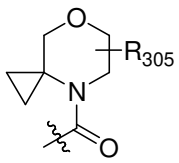
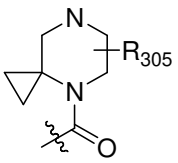
 and  .

In some embodiments of the present invention, R_{301} and R_{302}, together with the atom attached thereto, form a 4-8-membered saturated heterocyclic ring, which may be optionally substituted with one or more R_{305}, with R_{305} selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl.

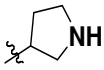
In some embodiments of the present invention, R_3 is  or  , and Ring J is a 4-8-membered saturated heterocyclic ring, which may be a monocyclic or bicyclic ring (including a fused or spiro ring), and optionally, which may include one or more other heteroatoms, and R_{305} is one or more independent substituents on Ring J, and is defined as those defined above.

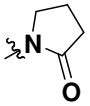
In some embodiments of the present invention, Ring J is  ,  , or .

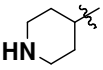
In some embodiments of the present invention, R_3 is selected from the group consisting of:  ,  ,

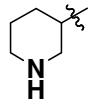





, , , , and .

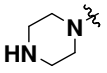
In some embodiments of the present invention, R_{305} is selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl (for example, methyl), halogenated C_1-C_6 alkyl (for example, -CHF_2, -CH_2F, or -CF_3), C_3-C_6 cycloalkyl (for example, , or), and 4-6-membered heterocycloalkyl (for example,

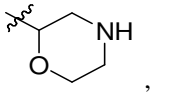










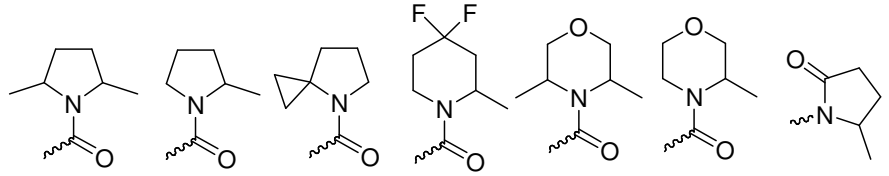


).

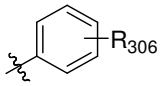
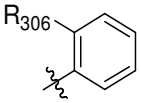
In some embodiments of the present invention, R_{305} is selected from the group consisting of: H, halogen (for example, F), C_1-C_3 alkyl, and C_1-C_3 halogenated alkyl.

In some embodiments of the present invention, R_{305} is selected from the group consisting of: H, F, -CH_3, -CHF_2, -CH_2F, and -CF_3.

In some embodiments of the present invention, R_3 is selected from the group consisting of:


.

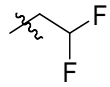
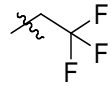
In some embodiments of the present invention, R_3 is -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), for example, phenyl, wherein the aryl (for example, phenyl) may be optionally substituted with one or more R_{306}, and R_{306} is selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl.

In some embodiments of the present invention, R_3 is  , and R_{306} is one or more independent substituents (in particular, ) on a benzene ring.

In some embodiments of the present invention, R_{306} is selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl (for example, methyl, ethyl, or isopropyl), halogenated C_1-C_6 alkyl (for example, -CHF_2, -CH_2F, or -CF_3), and C_3-C_6 cycloalkyl (for example, , or).

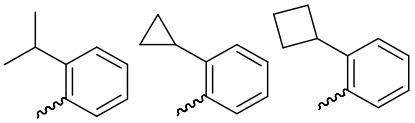
In some embodiments of the present invention, R_{306} is selected from the group consisting of: H, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, and C_3-C_4 cycloalkyl.

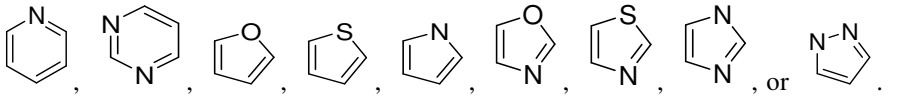
In some embodiments of the present invention, R_{306} is selected from the group consisting of: ,

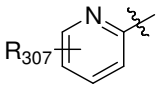



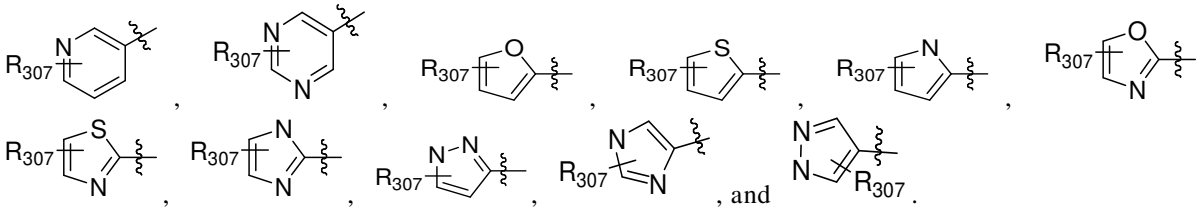
, and .

In some embodiments of the present invention, R_3 is selected from the group consisting of:



In some embodiments of the present invention, R_3 is -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), the 4-10-membered heterocyclyl may be optionally substituted with one or more R_{307}, and R_{307} is selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl. More specifically, the 4-10-membered heterocyclic ring may be  .

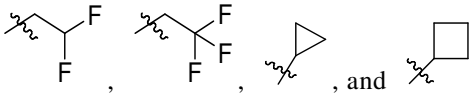
In some embodiments of the present invention, R_3 is selected from the group consisting of:  ,

 .

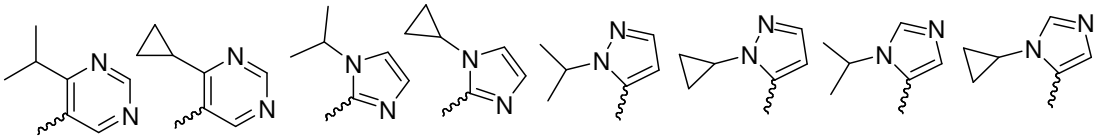
In some embodiments of the present invention, R_{307} is selected from the group consisting of: H, halogen (for example, F), C_1-C_6 alkyl (for example, methyl, ethyl, or isopropyl), halogenated C_1-C_6 alkyl (for example, -CHF_2, -CH_2F, or -CF_3), and C_3-C_6 cycloalkyl (for example, , or).

In some embodiments of the present invention, R_{307} is selected from the group consisting of: H, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, and C_3-C_4 cycloalkyl.

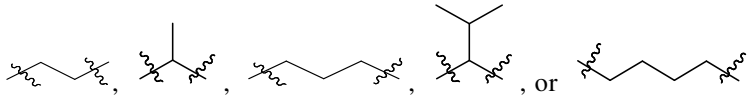
In some embodiments of the present invention, R_{307} is selected from the group consisting of: ,

 .

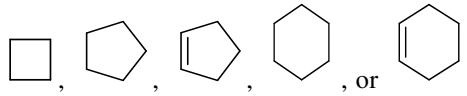
In some embodiments of the present invention, R_3 is selected from the group consisting of:

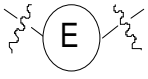
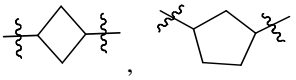
 .

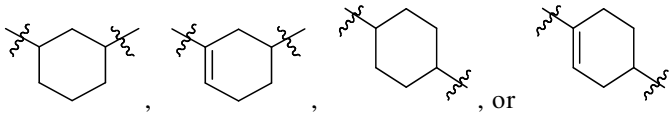
In some embodiments of the present invention, L_1 is a single bond.

In some embodiments of the present invention, L_1 is C_1-C_6 alkylene, in particular, C_1-C_4 alkylene, for example, methylene,  .

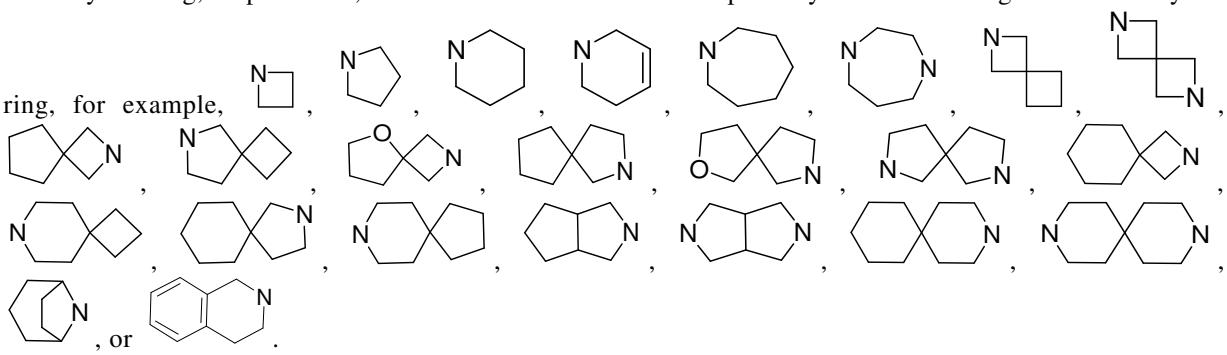
In some embodiments of the present invention, L_1 is -O-, -S- or -N(R_{La})-; more specifically, R_{La} may be selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl).

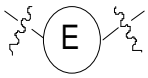
In some embodiments of the present invention, Ring E is a 3-8-membered saturated or partially saturated aliphatic ring , for example,  .

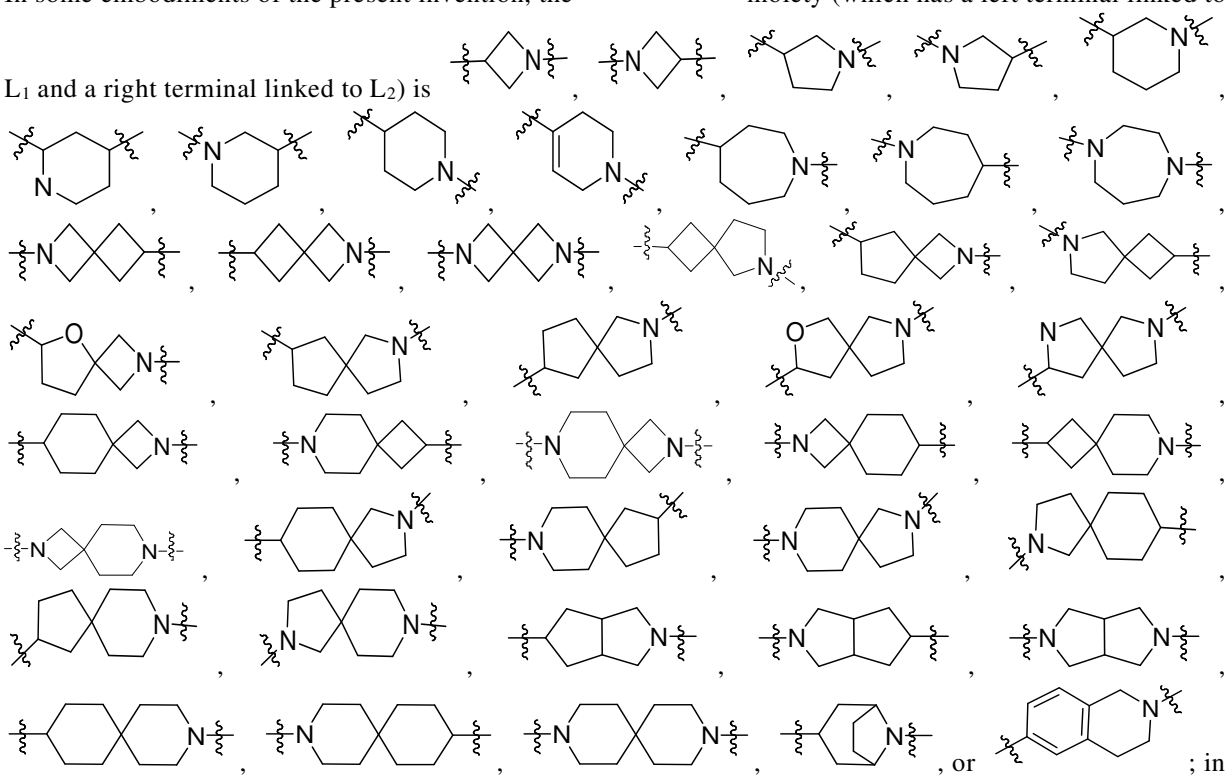
In some embodiments of the present invention, the  moiety is  ,



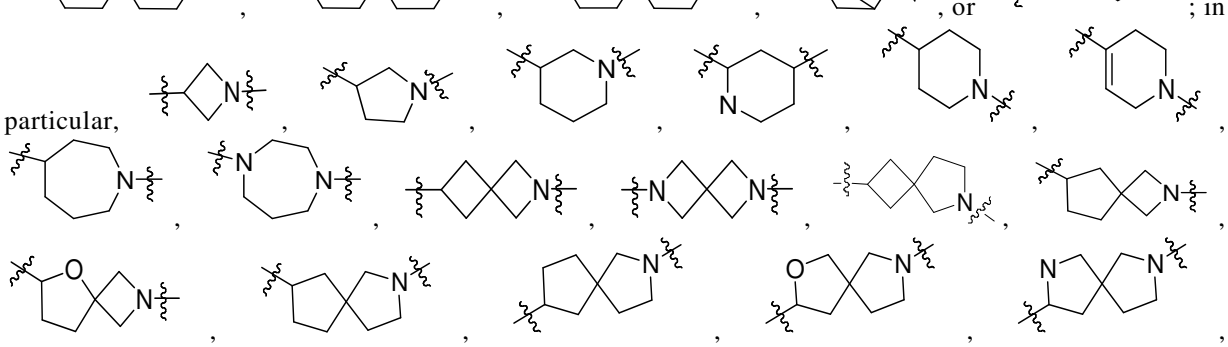
In some embodiments of the present invention, Ring E is a 4-12-membered saturated or partially saturated heterocyclic ring, in particular, a 4-10-membered saturated or partially saturated nitrogenous heterocyclic ring, for example,

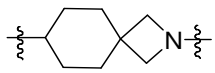
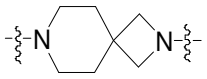
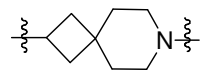
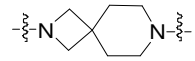
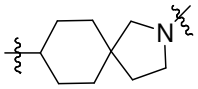
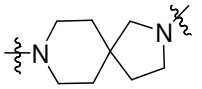
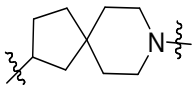
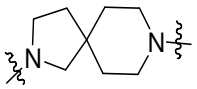
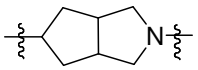
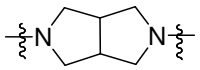
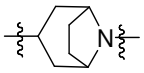
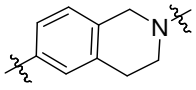
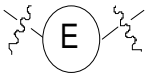
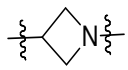
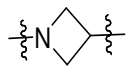
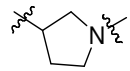
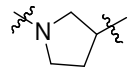
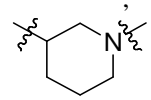
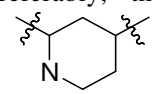
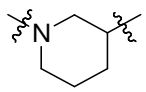
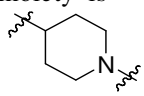
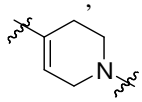
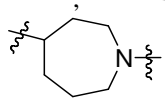
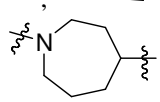
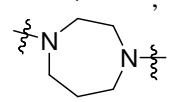


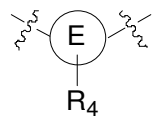
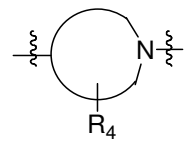
In some embodiments of the present invention, the  moiety (which has a left terminal linked to L_1 and a right terminal linked to L_2) is

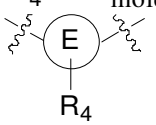
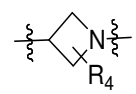
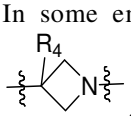


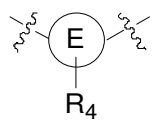
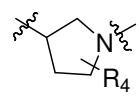
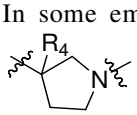
; in particular,



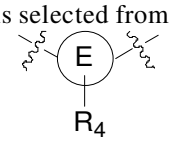
 ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,
, ,  , or  ; preferably, the  moiety is  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  , or  .

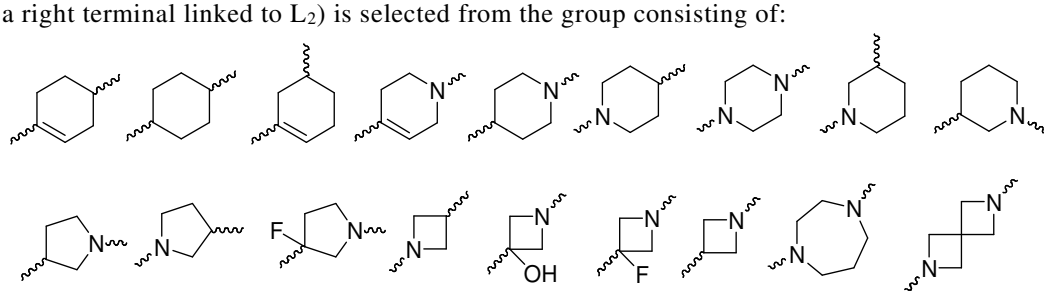
In some embodiments of the present invention, the  moiety is  .

In some embodiments of the present invention, the  moiety is  , in particular  .

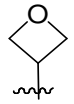
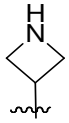
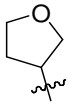
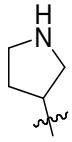
In some embodiments of the present invention, the  moiety is  , in particular  .

In some embodiments of the present invention, R_4 is selected from the group consisting of: H, halogen (for example, F), =O, cyano, nitro, azido, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, and C_1-C_6 cyanoalkyl.
In some embodiments of the present invention, R_4 is selected from the group consisting of: H, halogen (for example, F), hydroxyl, C_1-C_3 alkyl, and C_1-C_3 alkoxy.
In some embodiments of the present invention, R_4 is selected from the group consisting of: H, F and hydroxyl.

In some embodiments of the present invention, the  moiety (which has a left terminal linked to L_1 and a right terminal linked to L_2) is selected from the group consisting of:



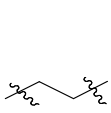
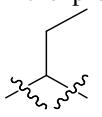
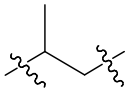
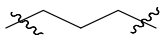
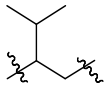
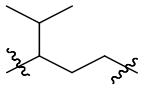
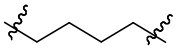
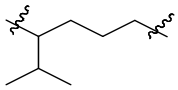
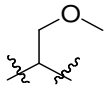
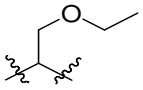
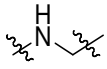
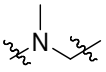
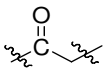
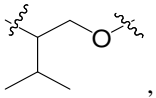
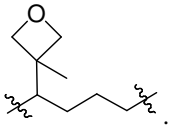
In some embodiments of the present invention, L_2 is a single bond.
In some embodiments of the present invention, L_2 is C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Q-(C_0-C_6 alkylene)-, wherein the H atom in the alkylene may be optionally substituted with a group selected from the group

consisting of: H, C_1-C_3 alkyl, halogen, cyano, halogenated C_1-C_3 alkyl, hydroxyl, C_1-C_3 alkoxy, halogenated C_1-C_3 alkoxy, amino, C_1-C_6 alkylamino, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl (for example,  ,  ,  , or ), C_1-C_3 alkyl-substituted 3-6-membered heterocyclyl (for example,).

In some embodiments of the present invention, Q is selected from the group consisting of: -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{La})-, -N(R_{La})C(O)-, -N(R_{La})C(O)O-, -N(R_{La})C(O)N(R_{La})-, -N(R_{La})-, -S(O)$_2$-, -S(O)$_2$N(R_{La})-, -N(R_{La})S(O)$_2$-, -S(O)-, -S(O)N(R_{La})-, -N(R_{La})S(O)-, -C(=NR_{La})-, and -C(=NR_{La})-NR_{La}-; wherein each R_{La} is independently selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl, or ethyl).

In some embodiments of the present invention, Q is selected from the group consisting of: -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{La})-, -N(R_{La})C(O)-, -N(R_{La})C(O)O-, -N(R_{La})-, -S(O)$_2$-, and -S(O)-; wherein each R_{La} is independently selected from the group consisting of: H and C_1-C_3 alkyl (for example, methyl, or ethyl).

In some embodiments of the present invention, Q is selected from the group consisting of: -O-, -C(O)-, -N(C_0-C_3 alkyl)-, and -N(C_0-C_3 alkyl)C(O)-.

In some embodiments of the present invention, L_2 is selected from the group consisting of: methylene,  , ,  ,  ,  , ,  ,  ,  ,  ,  ,  , -O-, -C(O)-, -NHC(O)-,  ,  ,  ,  , and  .

In some embodiments of the present invention, R^Y is R^{Y0}, which is selected from the group consisting of: H, =O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, -OR_7, -C(O)R_7, -C(O)OR_7, -NR_8C(O)OR_7, -OC(O)R_7, -NR_8S$O_2$$R_7$, -S$O_2NR_7$$R_8$, -N$R_7$C(O)$R_8$, -C(O)N$R_7$$R_8$, -N$R_7$$R_8$, -S$R_7$, -S(O)$R_7$, -S$(O)_2$$R_7$, -S$O_3$H, -($C_0$-$C_6$ alkylene)-(phenyl), -SO_2-(C_0-C_6 alkylene)-(phenyl), -S-(C_0-C_6 alkylene)-(phenyl), -O-(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), and the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl.

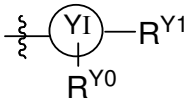
In some embodiments of the present invention, R^Y is R^{Y1}, which is selected from the group consisting of: H, -C(O)R_7, -C(O)OR_7, -NR_8S$O_2$$R_7$, -N$R_8$C(O)O$R_7$, -N$R_8$C(O)$R_7$, -C(O)N$R_7$$R_8$, -N$R_7$$R_8$, -S$(O)_2$$R_7$, C_1-C_6 alkyl, -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), and -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl); wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl; R_7 and R_8 are each independently selected from the group consisting of: H, C_1-C_6 alkyl, -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), and -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl); wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-

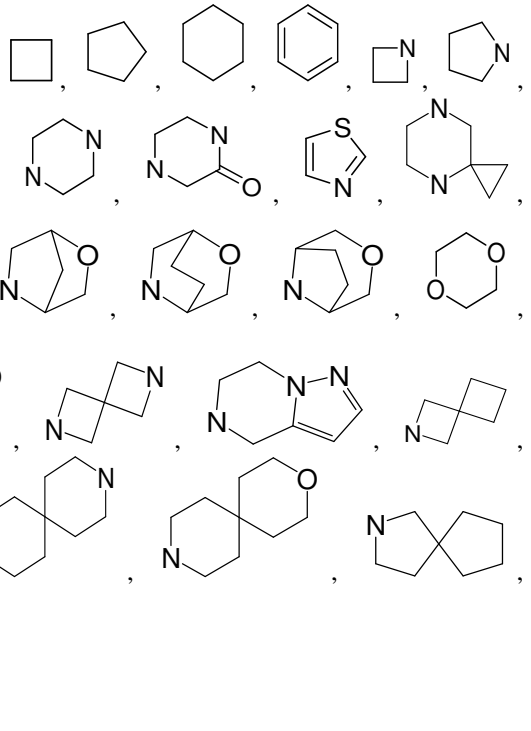
C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl.

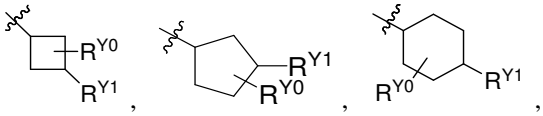
In some embodiments of the present invention, R^Y is R^{Y2}, which is selected from the group consisting of: H, cyano, C_1-C_6 alkyl, and 4-10-membered heterocyclyl, wherein the C_1-C_6 alkyl or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: =O, halogen, cyano, nitro, amino, 4-10-membered heterocyclyl, C_3-C_8 cycloalkyl, 4-10-membered heterocyclyl, -(C_0-C_4 alkylene)-OH, -(C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy, -C(O)O(C_0-C_6 alkyl), -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl), -N(C_0-C_6 alkyl)C(O) (C_0-C_6 alkyl), -SO_2(C_0-C_6 alkyl), -SO_2(phenyl), halogenated -SO_2(C_1-C_6 alkyl), -SO_2N(C_0-C_6 alkyl)(C_0-C_6 alkyl), -SO_2NH(phenyl), -NHSO_2(C_0-C_6 alkyl), -NHSO_2(phenyl) and -NHSO_2(C_1-C_6 halogenated alkyl); and in R^{Y2}, the cycloalkyl or heterocyclyl may be further optionally substituted with a substituent selected from the group consisting of: C_1-C_4 alkyl, and halogenated C_1-C_4 alkyl.

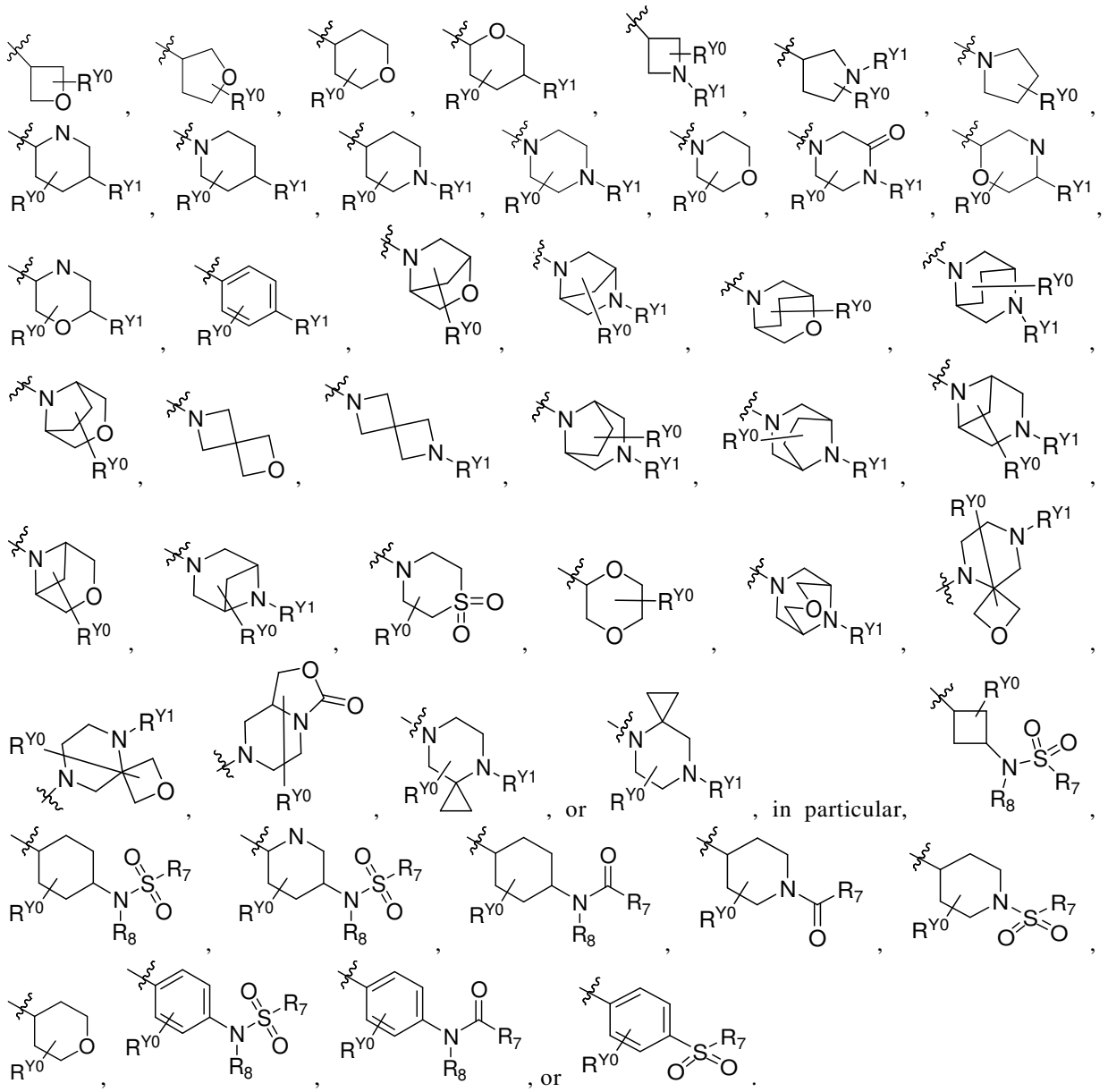
In some embodiments of the present invention, R^Y is R^{Y3}, which is selected from the group consisting of: H, =O, , C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), and -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl); wherein the C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl.

Specifically, Y is selected from groups in sets Y1, Y2, Y3, Y4, and Y5.

In some embodiments of the present invention, Y1 is  , wherein Ring YI is a 3-8-membered saturated or partially saturated aliphatic ring, a benzene ring, or a 4-12-membered saturated or partially saturated heterocyclic ring, and R^{Y0} is one or more independent substituents on a ring, and is defined as above in the present invention.

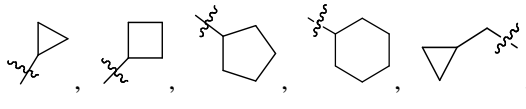
In some embodiments of the present invention, Ring YI is  .

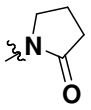
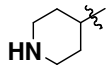
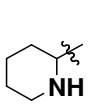
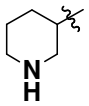
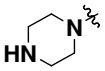
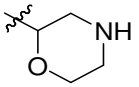
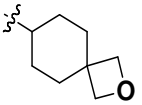
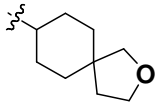
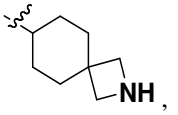
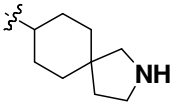
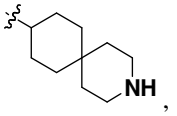
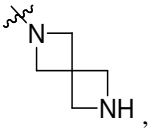
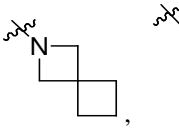
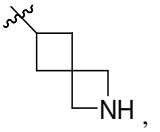
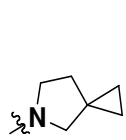
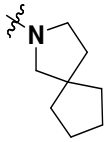
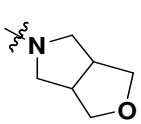
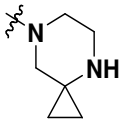
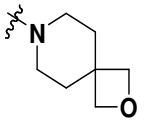
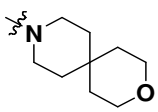
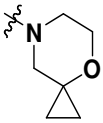
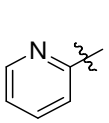
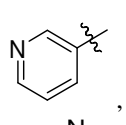
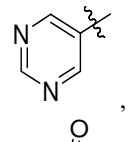
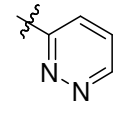
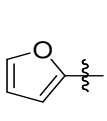
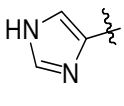
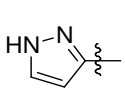
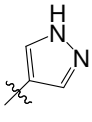
In some embodiments of the present invention, Y1 is  ,



In some embodiments of the present invention, in Y1, R^{Y0} is selected from the group consisting of: H, halogen (for example, F), C_1-C_3 alkyl (for example, methyl), halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy.

In some embodiments of the present invention, R^{Y1} is selected from the group consisting of: $-NR_8SO_2R_7$, $-NR_8C(O)OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(O)NR_7R_8$, $-S(O)_2R_7$, C_1-C_6 alkyl, and $-(C_0$-C_3 alkylene)(4-10-membered heterocyclyl), wherein the C_1-C_6 alkyl or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, hydroxyl-substituted C_1-C_6 alkyl, $-C(O)N(C_0$-C_6 alkyl)(C_0-C_6 alkyl), and $-N(C_0$-C_6 alkyl)$C(O)(C_0$-C_6 alkyl).

In some embodiments of the present invention, R_7 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl, ethyl, n-propyl, or isopropyl), halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, $-(C_0$-C_3 alkylene)-(C_3-C_6 cycloalkyl) (for example, ), and $-(C_0$-C_3 alkylene)-(4-10-membered heterocyclyl) (the 4-10-membered heterocyclyl is, for

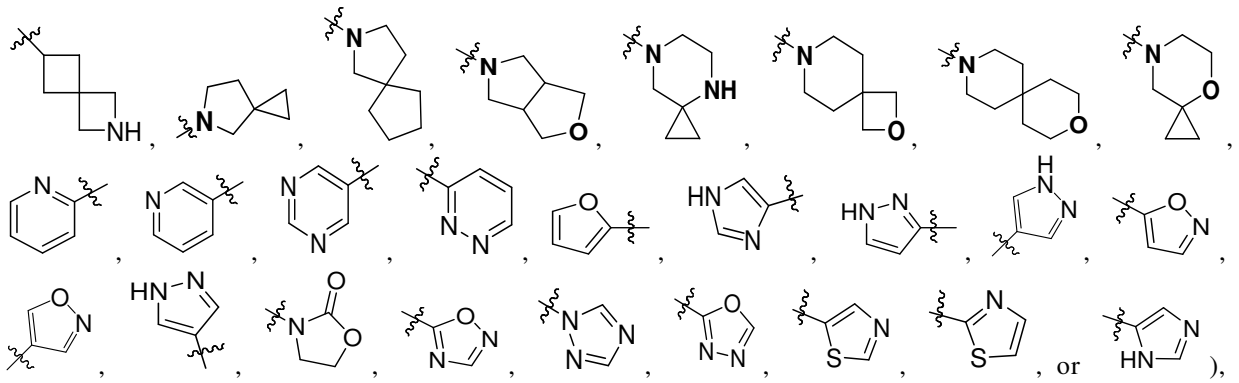
example, , , , , , ,  , ,  ,  ,  , ,  , ,  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or), wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, hydroxyl-substituted C_1-C_6 alkyl, -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl), and -N(C_0-C_6 alkyl)C(O)(C_0-C_6 alkyl).

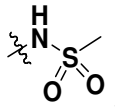
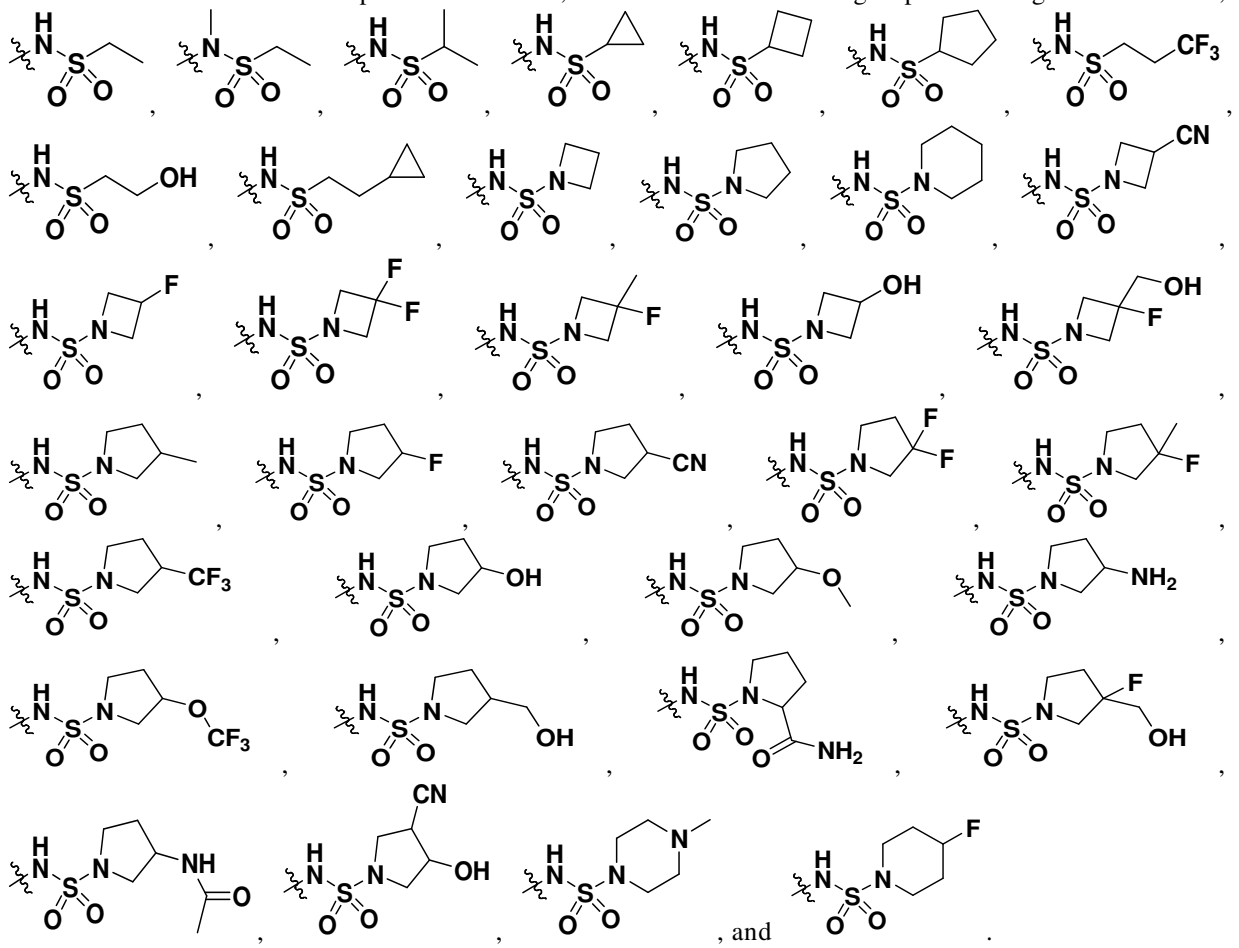
In some embodiments of the present invention, R_7 is selected from the group consisting of: C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_3 alkylene)-(C_3-C_6 cycloalkyl), 4-10-membered heterocyclyl, and -(C_1-C_3 alkylene)-(4-10-membered heterocyclyl).

In some embodiments of the present invention, R_8 is selected from H and $C_{1\text{-}6}$ alkyl (for example, methyl).

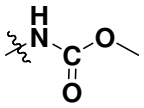
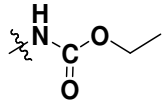
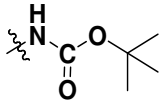
In some embodiments of the present invention, R_8 is H.

In some embodiments of the present invention, R^{Y1} is -$NR_8SO_2R_7$, wherein R_7 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl, ethyl, n-propyl, or isopropyl), halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, C_3-C_6 cycloalkyl (for example, , , , or), -(C_1-C_3 alkylene)-(C_3-C_6 cycloalkyl) (for example, , or), and 4-10-membered heterocyclyl (for example, ,

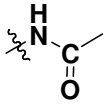
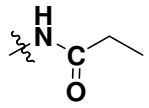
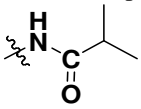

, wherein the 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, hydroxyl-substituted C_1-C_6 alkyl, -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl), and -N(C_0-C_6 alkyl)C(O)(C_0-C_6 alkyl); and R_8 is selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl).

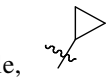
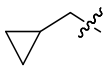
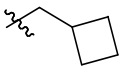
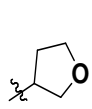
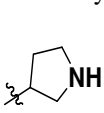
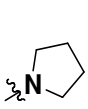
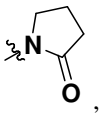
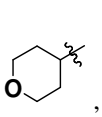
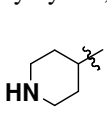
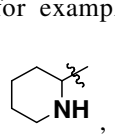
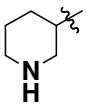
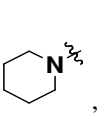
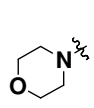
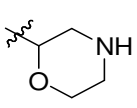
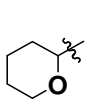
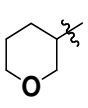
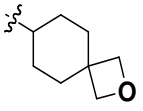
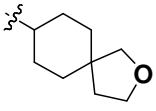
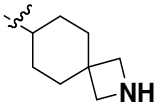
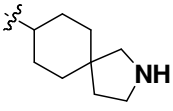
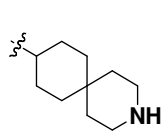
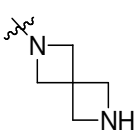
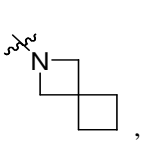
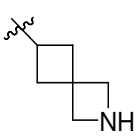
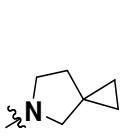
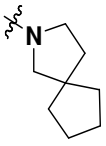
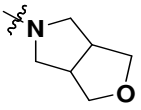
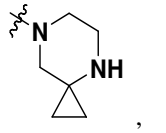
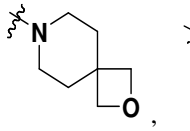
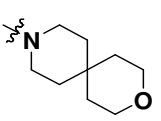
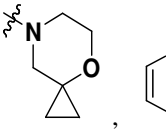
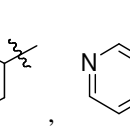
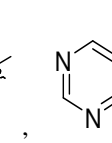
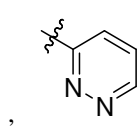
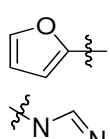
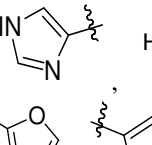
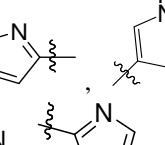
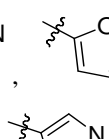
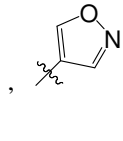
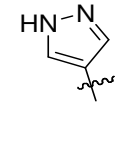
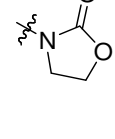
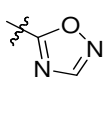
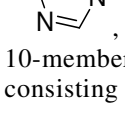
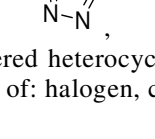
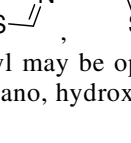
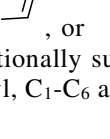
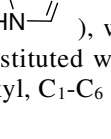
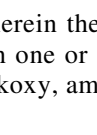
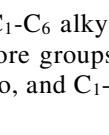
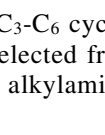
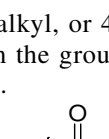
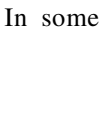
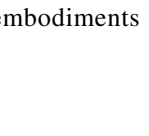
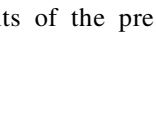
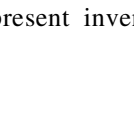
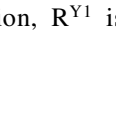
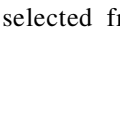
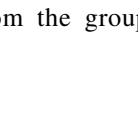
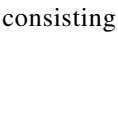
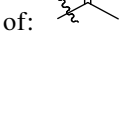
In some embodiments of the present invention, R^{Y1} selected from the group consisting of:  ,

, and .

In some embodiments of the present invention, R^{Y1} is -$NR_8C(O)OR_7$, wherein R_7 is selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl, ethyl, n-propyl, isopropyl, or tert-butyl), and R_8 is selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl).

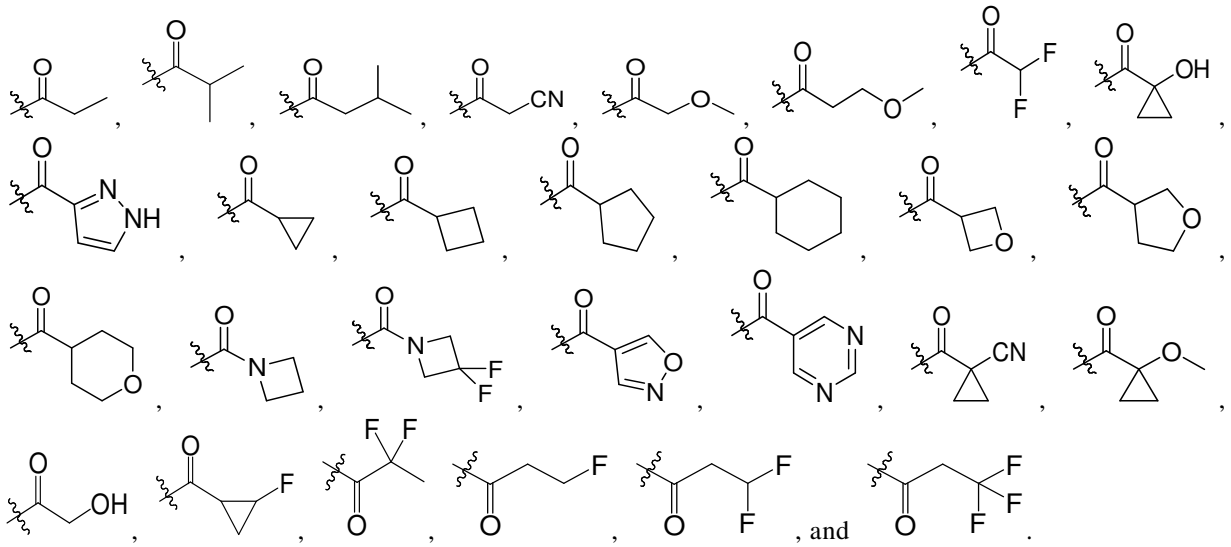
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of:  ,  , and  .

In some embodiments of the present invention, R^{Y1} is $-NR_8C(O)R_7$, wherein R_7 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl, ethyl, n-propyl, isopropyl, or tert-butyl), and halogenated C_1-C_6 alkyl, and R_8 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl).

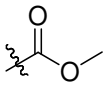
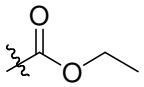
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of:  ,  , and  .

In some embodiments of the present invention, R^{Y1} is $-C(O)R_7$, wherein R_7 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl, or ethyl), -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl) (for example,  , , , ,  , or ), and -(C_0-C_3 alkylene)-(4-10-membered heterocyclyl) (the 4-10-membered heterocyclyl is, for example, , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , or), wherein the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and C_1-C_6 alkylamino.

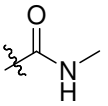
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of: ,

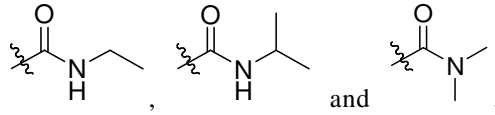


In some embodiments of the present invention, R^{Y1} is $-C(O)R_7$, wherein R_7 is selected from the group consisting of: H and C1-C6 alkyl (for example, methyl, or ethyl).

In some embodiments of the present invention, R^{Y1} is selected from the group consisting of:  and  .

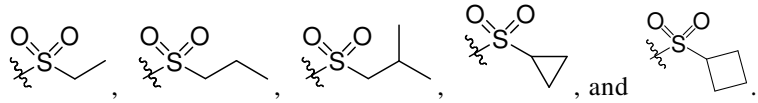
In some embodiments of the present invention, R^{Y1} is $-C(O)NR_7R_8$, wherein R_7 is selected from the group consisting of: H, C_1-C_6 alkyl (for example, methyl, or ethyl), and C_3-C_6 cycloalkyl (for example, cyclopropyl), and R_8 is selected from H and C_1-C_6 alkyl (for example, methyl).

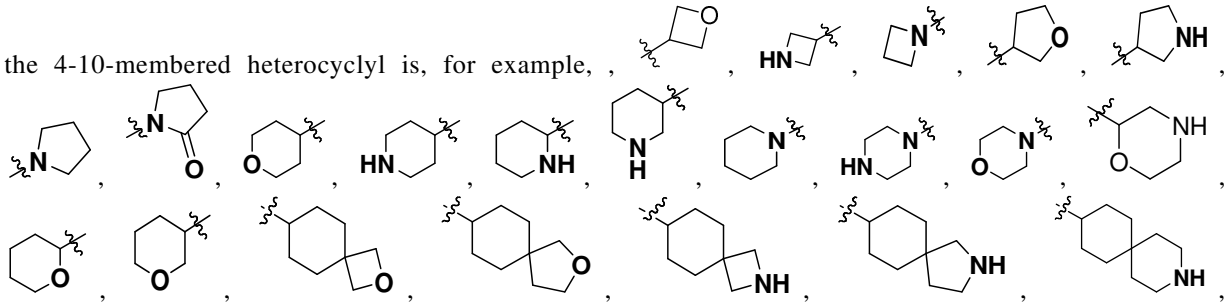
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of:  ,

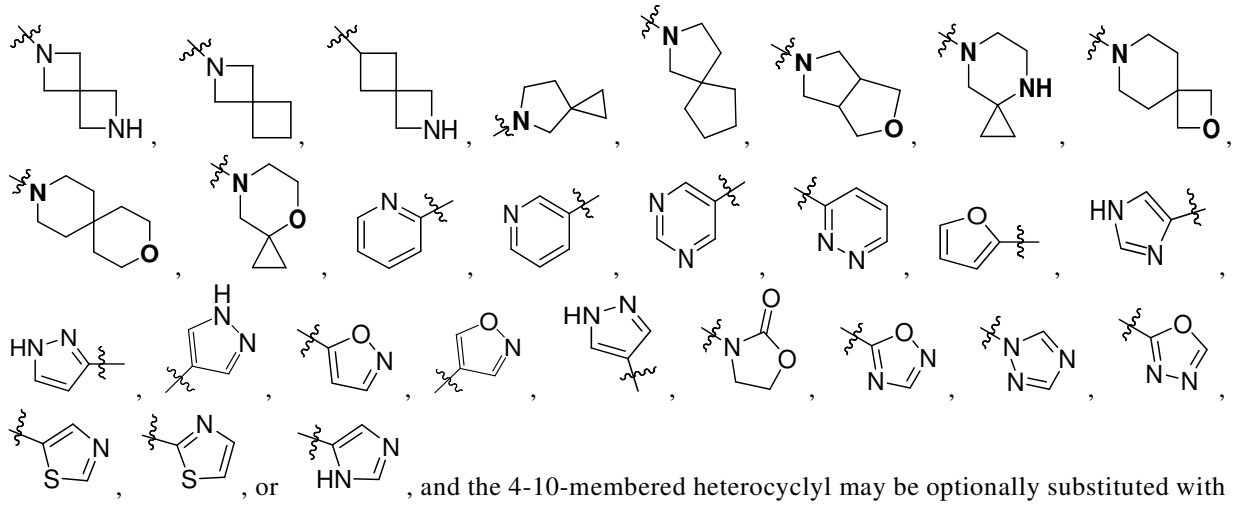


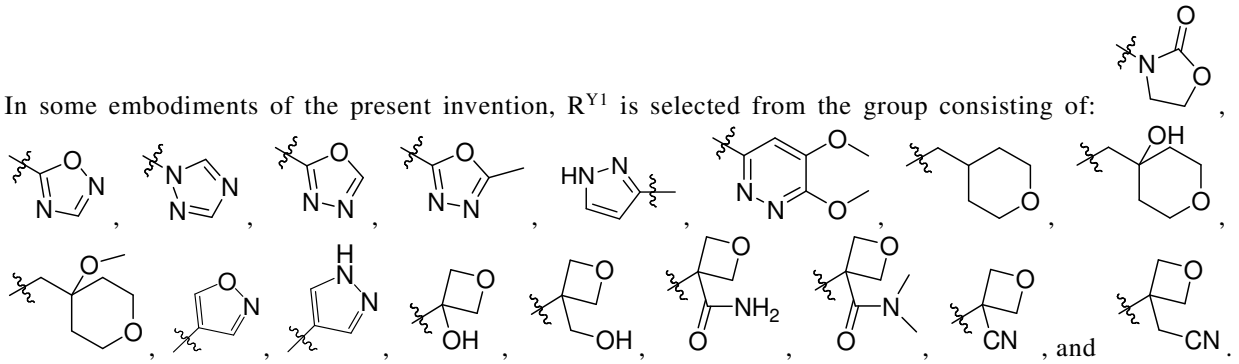
In some embodiments of the present invention, R^{Y1} is $-S(O)_2R_7$, wherein R_7 is selected from the group consisting of: H, C1-C6 alkyl (for example, methyl, or ethyl), and C_3-C_6 cycloalkyl (for example, cyclopropyl).

In some embodiments of the present invention, R^{Y1} is selected from the group consisting of: ,



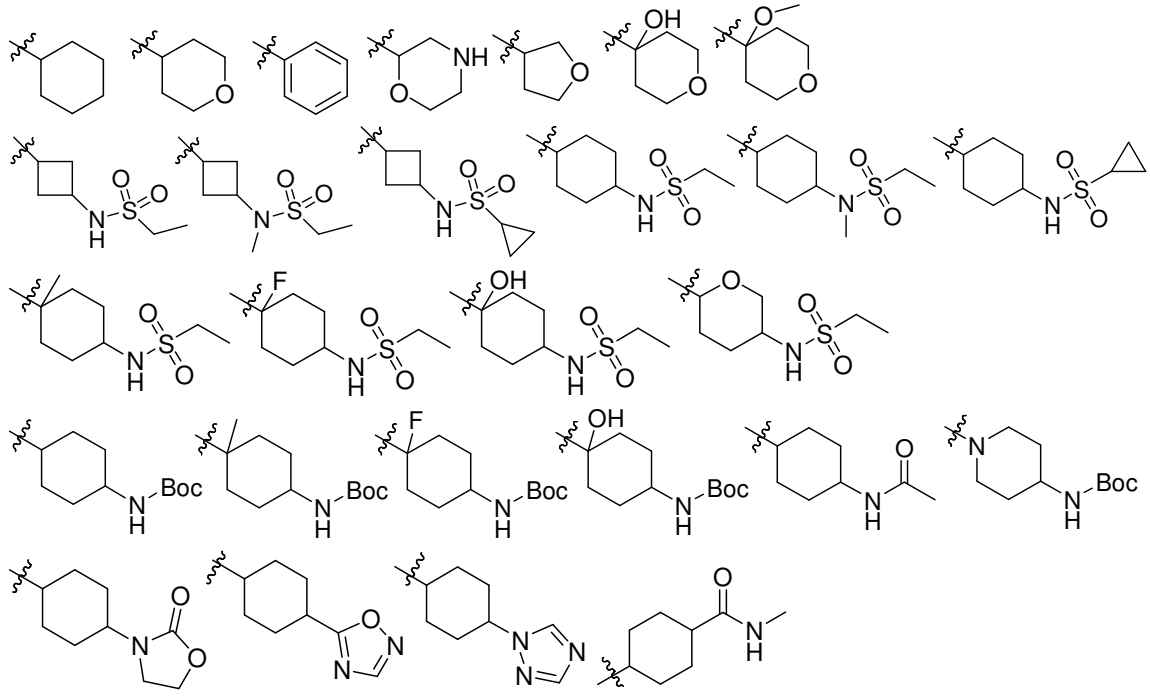
In some embodiments of the present invention, R^{Y1} is $-(C_0$-C_3 alkylene)(4-10-membered heterocyclyl), and the 4-10-membered heterocyclyl is, for example, 

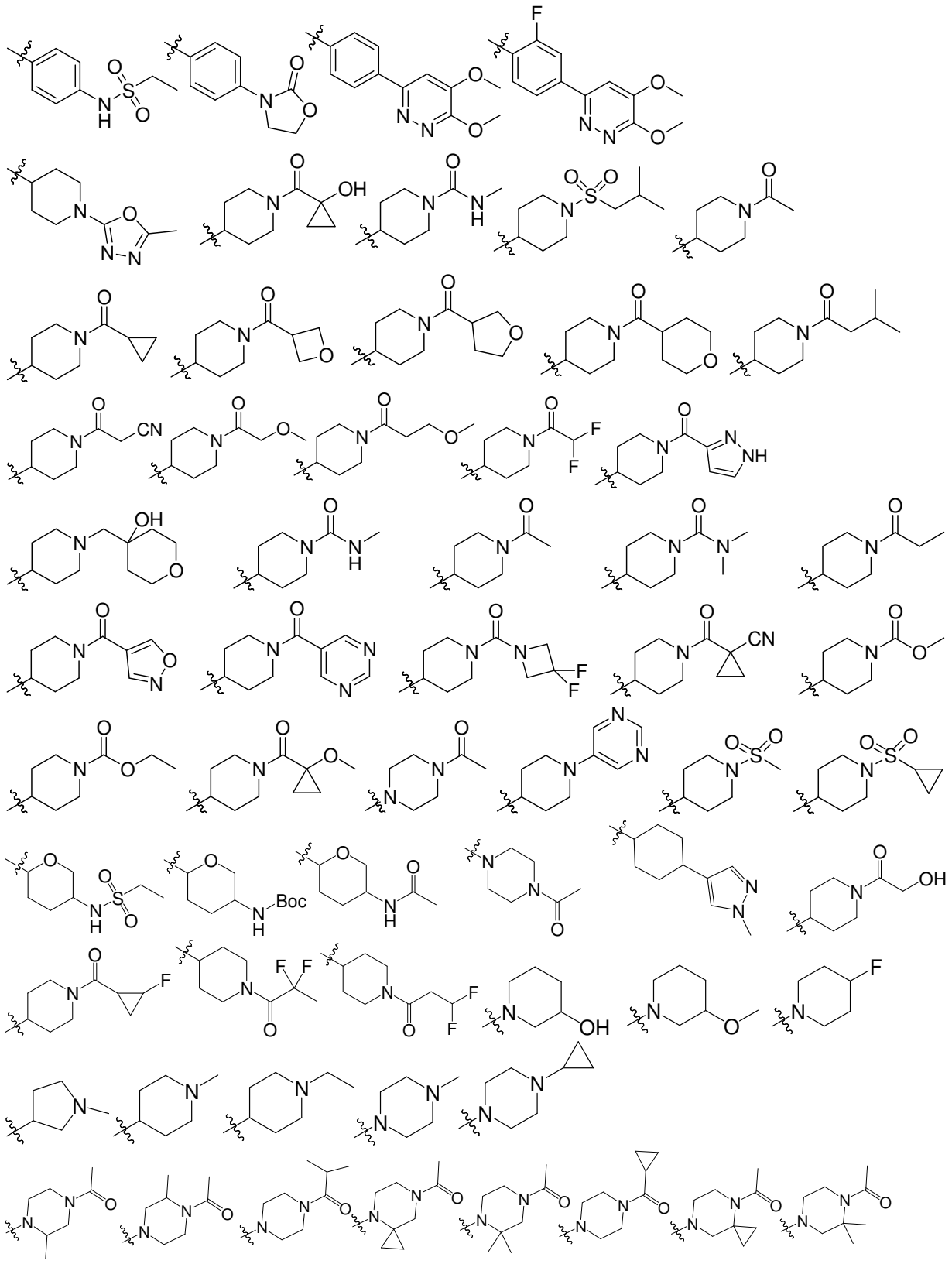

, and the 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and C_1-C_6 alkylamino.

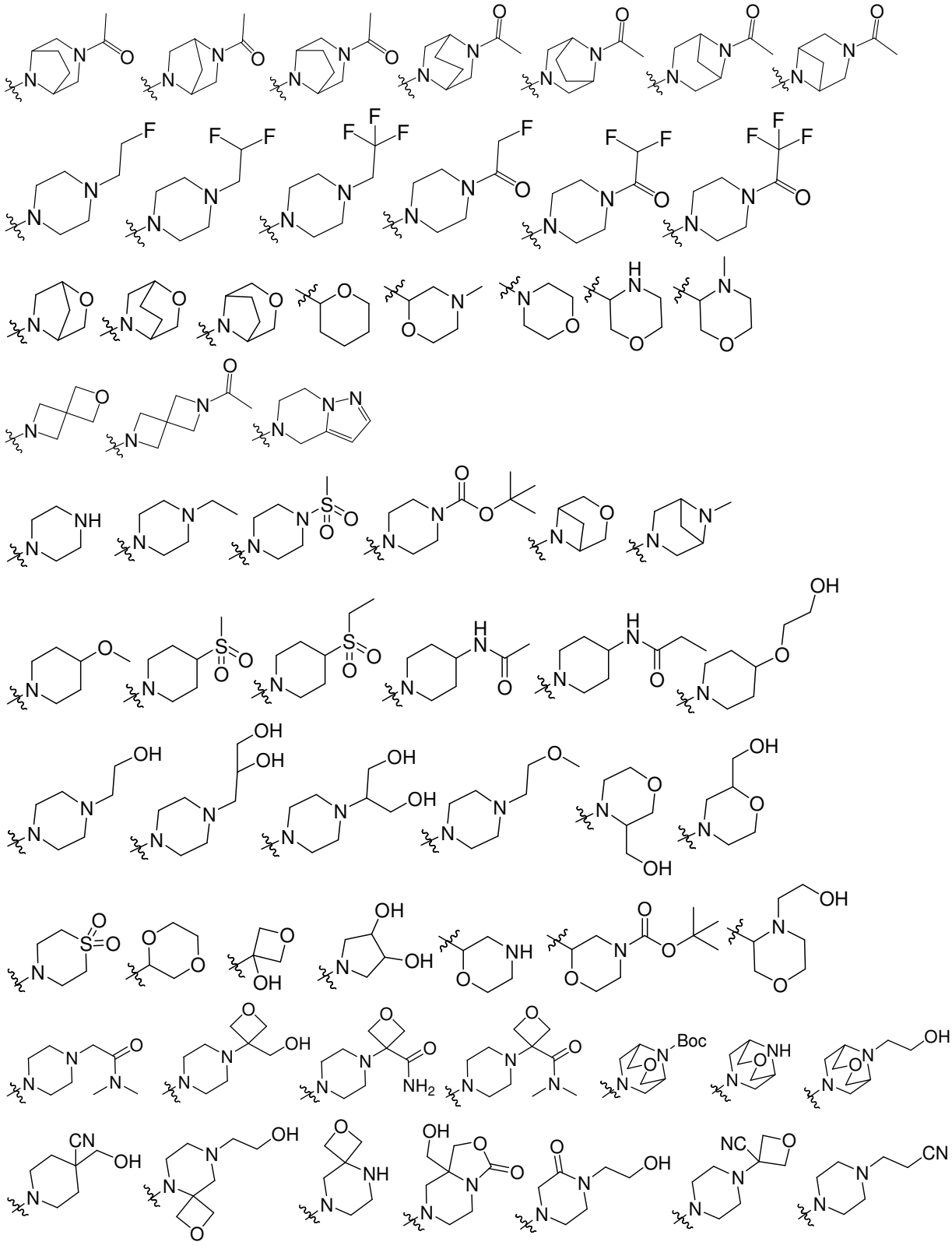
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of:

.

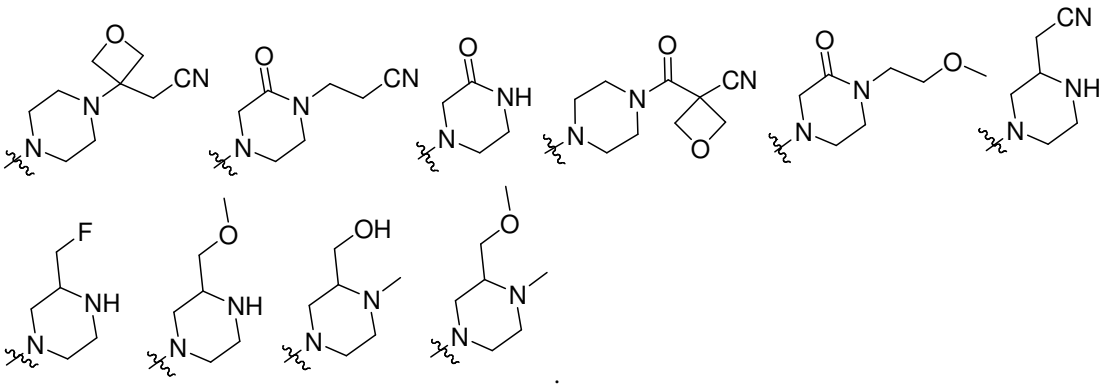
In some embodiments of the present invention, R^{Y1} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, C_1-C_6 alkoxyalkyl, -O-(hydroxyl-substituted C_1-C_6 alkyl), -O-(C_1-C_6 alkoxyalkyl), and C_1-C_6 cyanoalkyl.

In some embodiments of the present invention, Y1 is selected from the group consisting of:

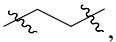
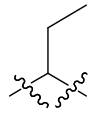
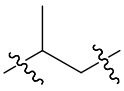
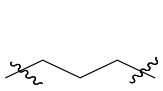
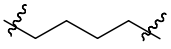
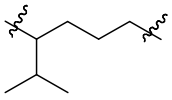
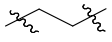
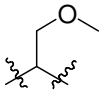
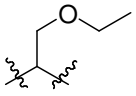
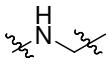
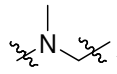
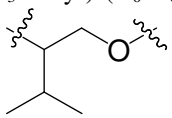


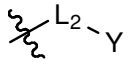


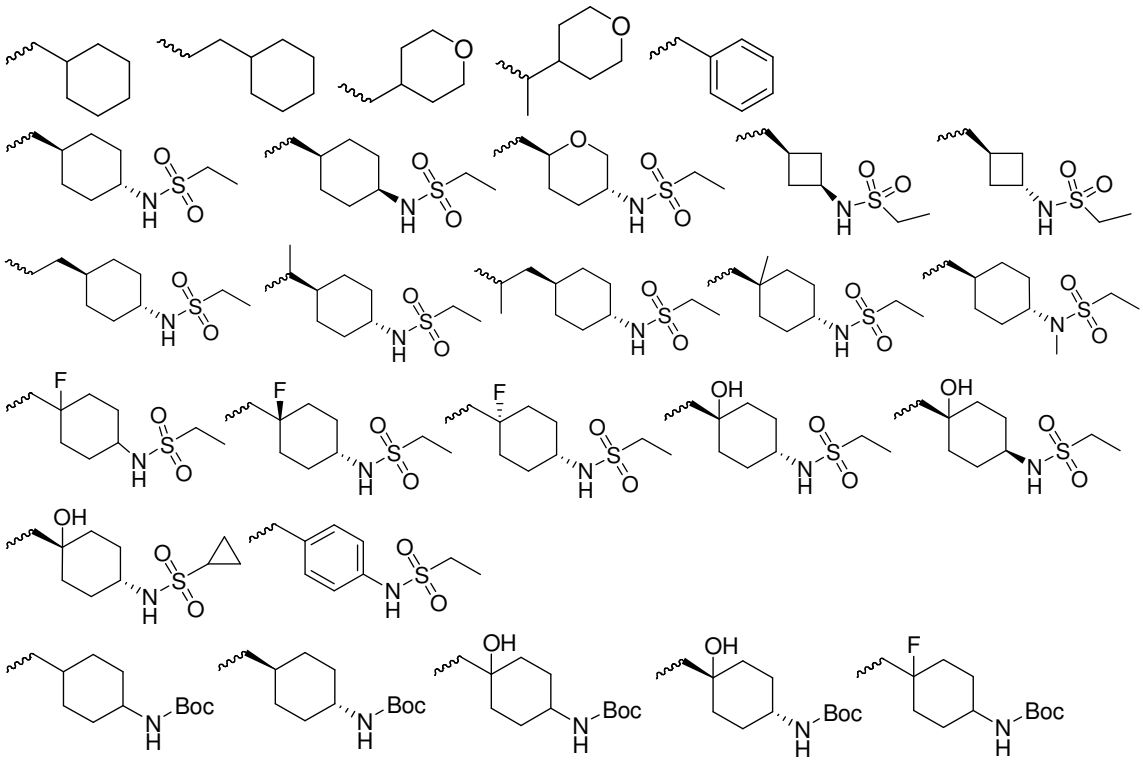


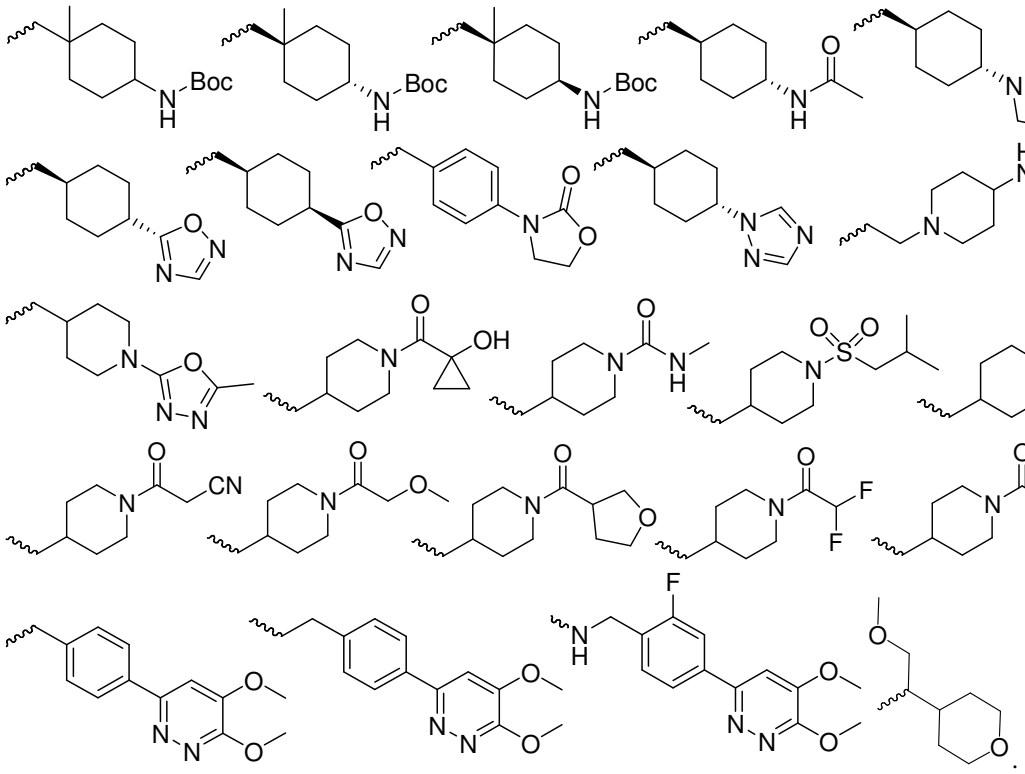


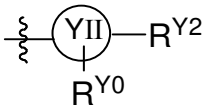
.

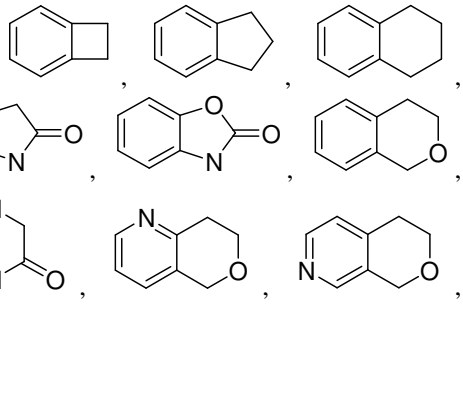
In some embodiments of the present invention, L_2 is C_1-C_6 alkylene (for example, methylene,  , ,  ,  ,  , ,  , or  , in particular, straight-chain alkylene, for example, methylene, or ), alkoxy-substituted C_1-C_6 alkylene (for example,  , or ) or -N(C_0-C_3 alkyl)-(C_0-C_6 alkylene)- (for example,  , or ), or -(C_0-C_6 alkylene)-O- (for example, ), and Y is Y1.

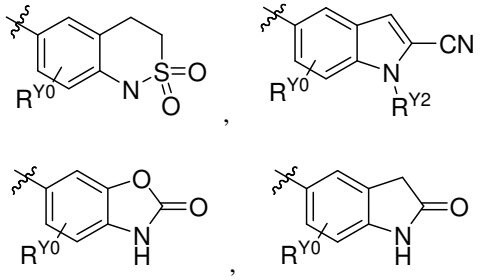
In some embodiments of the present invention, the  moiety is selected from the group consisting of:

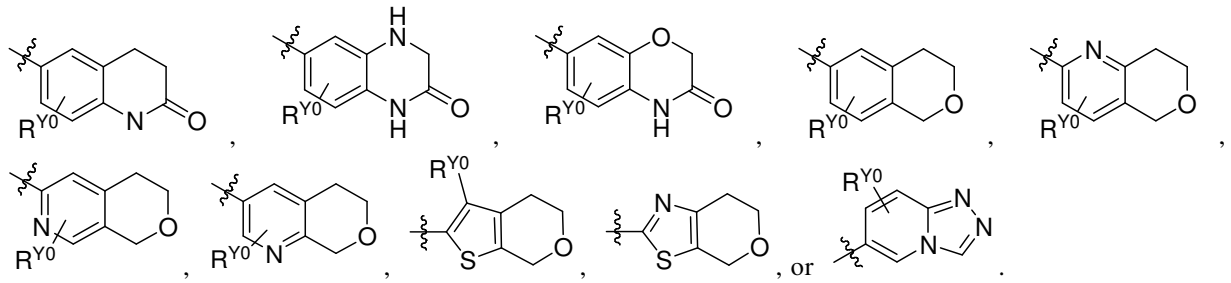




In some embodiments of the present invention, Y2 is  , wherein Ring YII is a benzene ring-fused four- to eight-membered aliphatic ring, a benzene ring-fused four- to eight-membered heterocyclic ring, or a bicyclic heterocyclic ring, and R^{Y0} is one or more independent substituents on a ring, and is defined as above in the present invention.

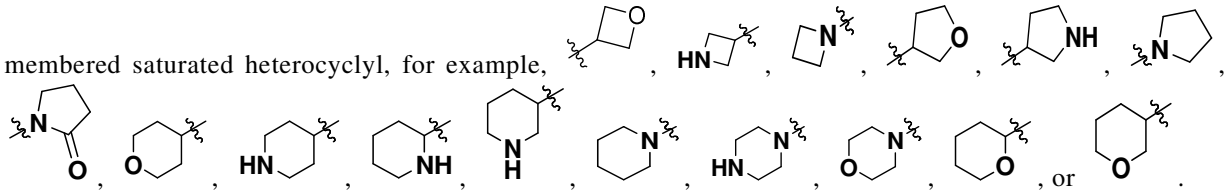
In some embodiments of the present invention, Ring YII is  .

In some embodiments of the present invention, Y2 is  .

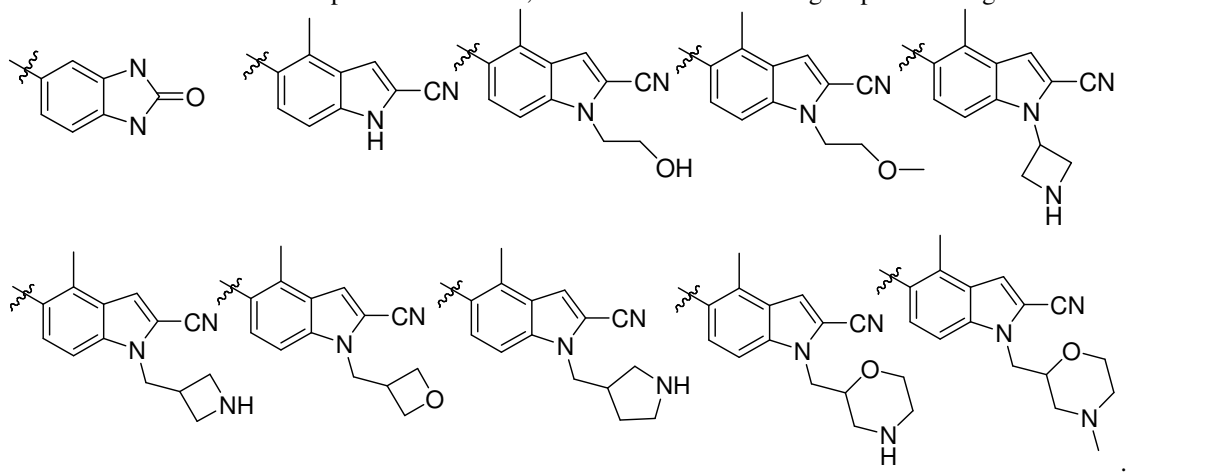


In some embodiments of the present invention, in Y2, R^{Y0} is selected from the group consisting of: H, halogen (for example, F), C_1-C_3 alkyl (for example, methyl), halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy, in particular, H or methyl.

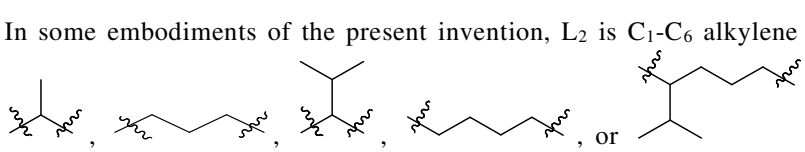
In some embodiments of the present invention, R^{Y2} is selected from the group consisting of: H, -(C_1-C_4 alkylene)-OH, -(C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -(C_0-C_4 alkylene)-(C_3-C_6 cycloalkyl), and -(C_0-C_4 alkylene)-(optionally substituted 4-10-membered heterocyclyl); and the 4-10-membered heterocyclyl is 4-6-membered saturated heterocyclyl, for example,



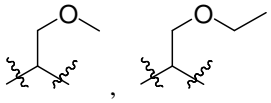
In some embodiments of the present invention, Y2 is selected from the group consisting of:



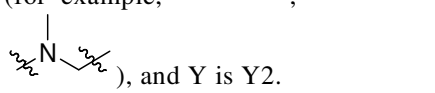
In some embodiments of the present invention, L_2 is C_1-C_6 alkylene (for example, methylene,



), alkoxy-substituted C_1-C_6 alkylene (for example,

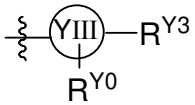


) or -N(C_0-C_3 alkyl)-(C_0-C_6 alkylene)- (for example,



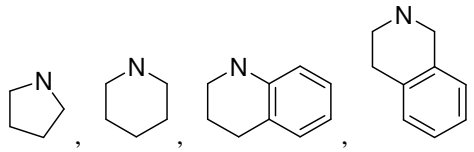
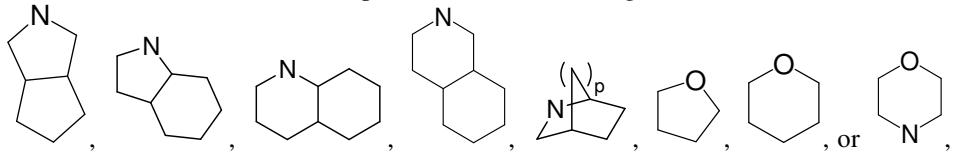
), and Y is Y2.

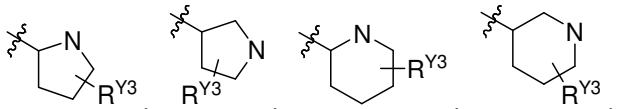
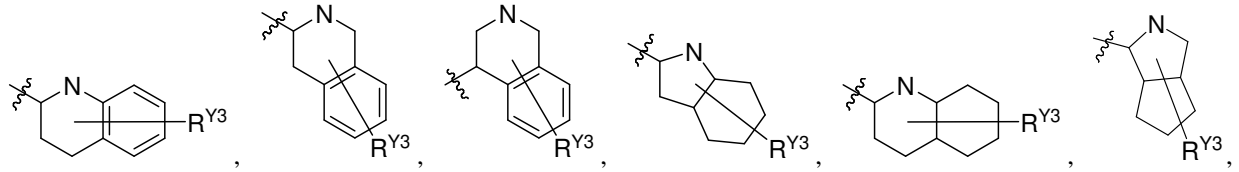
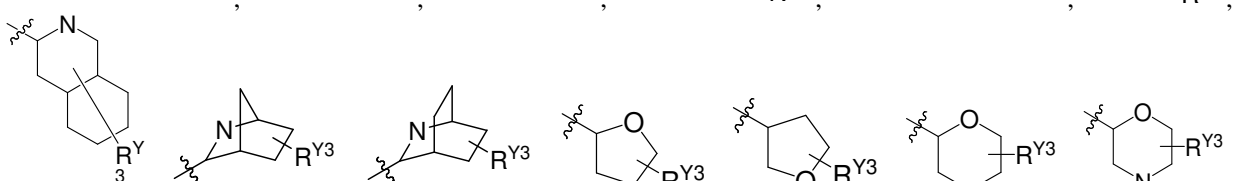
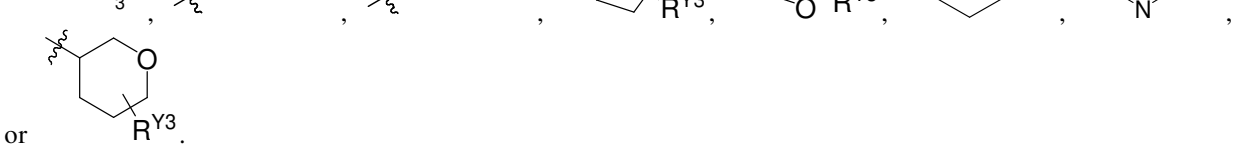
In some embodiments of the present invention, Y3 is



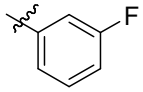
, wherein Ring YIII is a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring, a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring-fused benzene ring, a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring-fused four- to eight-membered aliphatic ring, or a six- to ten-membered bridged nitrogenous saturated heterocyclic ring, and R^{Y0} is one or more independent substituents

on the ring, and is defined as above in the present invention.

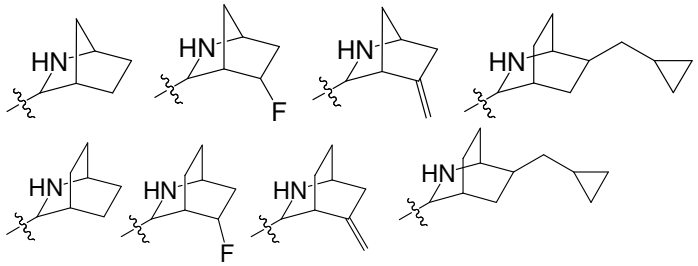
In some embodiments of the present invention, Ring YIII is  ,  , or , wherein p is 1 or 2.

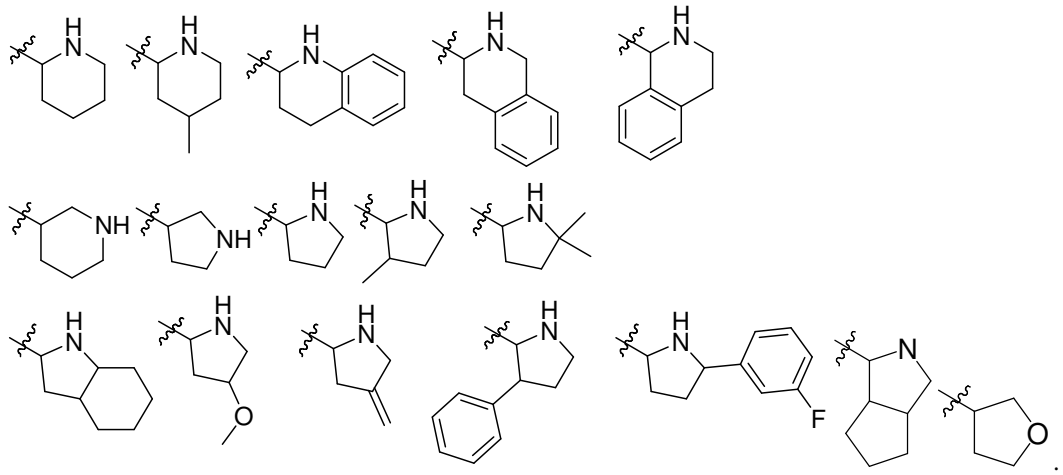
In some embodiments of the present invention, Y3 is  ,  ,  ,  , or .

In some embodiments of the present invention, in Y3, R^{Y0} is selected from the group consisting of: H, halogen (for example, F), C_1-C_3 alkyl (for example, methyl), halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy, in particular H.

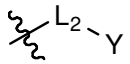
In some embodiments of the present invention, R^{Y3} is selected from the group consisting of: H, (for example,), halogen (for example, F), C_1-C_6 alkyl (for example, methyl), C_1-C_6 alkoxy (for example, methoxy), phenyl, and halogenated phenyl (for example, ).

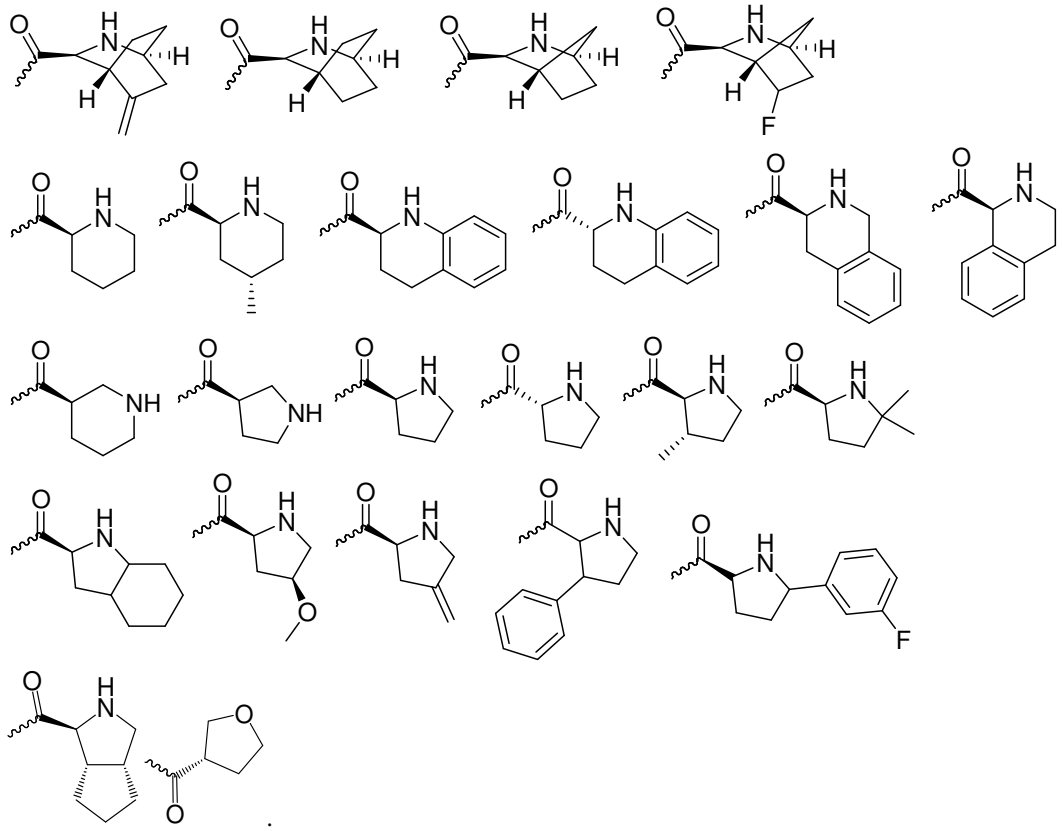
In some embodiments of the present invention, Y3 is selected from the group consisting of:

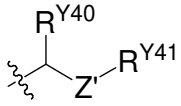




In some embodiments of the present invention, L_2 is C(O), and Y is Y3.

In some embodiments of the present invention, the  moiety is selected from the group consisting of:



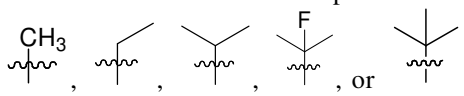
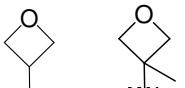
In some embodiments of the present invention, Y4 is  , wherein,

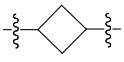
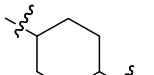
R^{Y40} is selected from the group consisting of: C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, and C_1-C_3 alkyl-substituted 3-6-membered heterocyclyl;

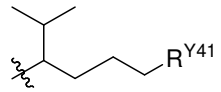
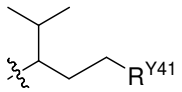
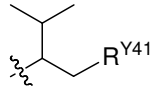
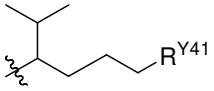
Z' is selected from the group consisting of: C_0-C_6 alkylene, -(C_0-C_3 alkylene)-O-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-S-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-C(O)NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NHC(O)-(C_0-C_3 alkylene)-, and C_3-C_6 cycloalkylene; wherein H in said alkylene is optionally substituted with one or more groups selected from the group consisting of: halogen,

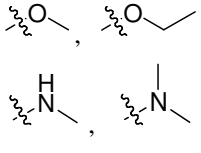
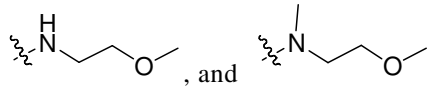
cyano, hydroxyl, and amino;

R^{Y41} is selected from the group consisting of: H, halogen, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4-12-membered heterocyclyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl); wherein H in the alkyl, cycloalkyl, aryl, or heterocyclyl is optionally substituted with a group selected from the group consisting of: halogen, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 4-12-membered heterocyclyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)CO(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)CON(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)SO_2(4-10-membered heterocyclyl), -O(4-10-membered heterocyclyl), -S(4-10-membered heterocyclyl), -SO(4-10-membered heterocyclyl), -SO_2(4-10-membered heterocyclyl), -SO_2N($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), -COO(4-10-membered heterocyclyl), -OCO(4-10-membered heterocyclyl), -CON($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), and -CO(4-10-membered heterocyclyl), wherein H in the alkyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 hydroxyl alkyl, C_1-C_6 alkoxyalkyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl).

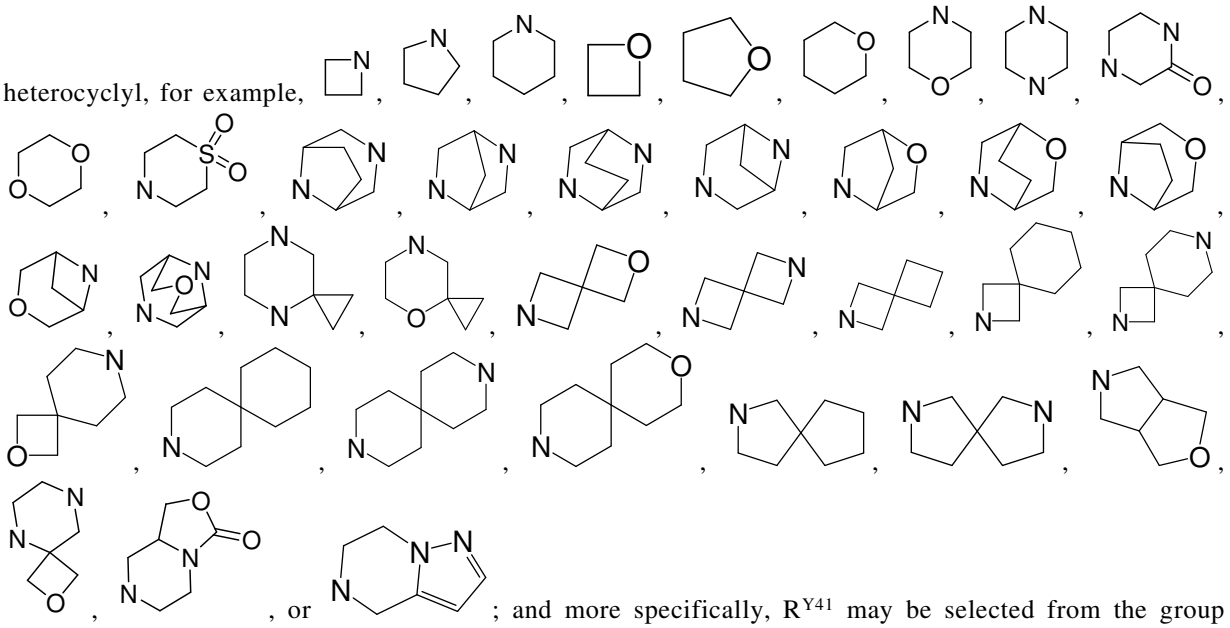
In some embodiments of the present invention, R^{Y40} is C_1-C_4 alkyl or halogenated C_1-C_4 alkyl, for example,  ; in some embodiments of the present invention, R^{Y40} is optionally substituted with C_1-C_3 alkyl-substituted 3-6-membered heterocyclyl, for example,  ; and in some embodiments of the present invention, R^{Y40} is C_3-C_6 cycloalkyl, for example, cyclopropyl, or cyclobutyl.

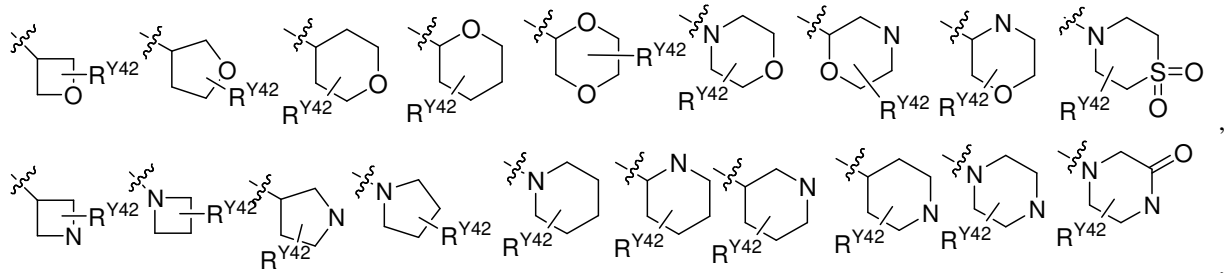
In some embodiments of the present invention, Z' is a single bond or C_1-C_6 alkylene, in particular straight-chain C_1-C_4 alkylene, wherein H in the alkylene is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, and hydroxyl. In some embodiments of the present invention, Z' is C_3-C_6 cycloalkylene, for example,  ; in particular,  .

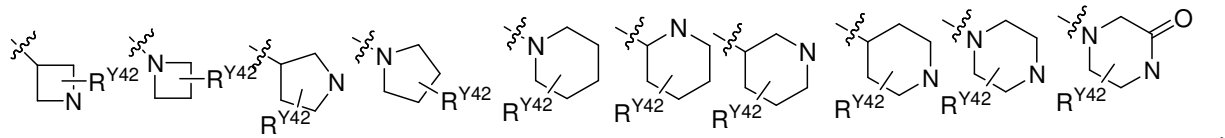
In some embodiments of the present invention, Y4 is  ,  , or  ; in particular,  .

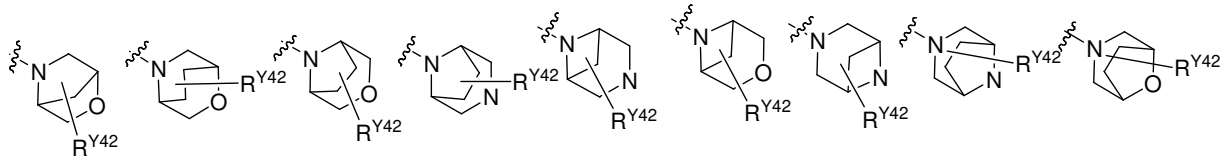
In some embodiments of the present invention, R^{Y41} is selected from the group consisting of: -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), and -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl); wherein H in the alkyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkoxy; more specifically, R^{Y41} is selected from the group consisting of: -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), and -COO($C_{0\text{-}10}$ alkyl); wherein H in the alkyl is optionally substituted with one or more groups selected from the group consisting of: hydroxyl and C_1-C_3 alkoxy. In some embodiments of the present invention, R^{Y41} is selected from the group consisting of: OH,  , and  .

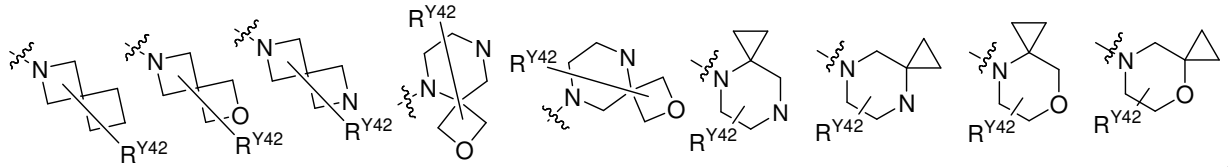
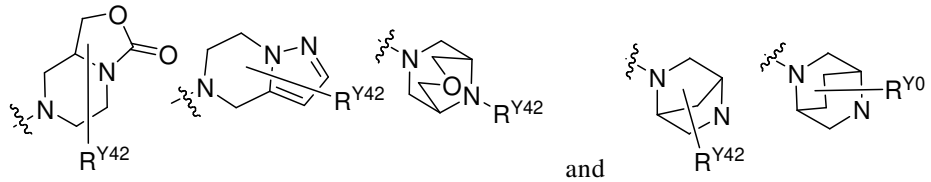
In some embodiments of the present invention, R^{Y41} is 4-12-membered heterocyclyl, H in the heterocyclyl is optionally substituted with one or more R^{Y42}, with each R^{Y42} independently selected from the group consisting of: H, C_1-C_6 alkyl, C_1-C_6 halogenated alkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_3-C_6 cycloalkyl, 4-6-membered saturated heterocyclyl, -N(C_{0-6} alkyl)(C_{0-6} alkyl), -N(C_{0-6} alkyl)CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)CON(C_{0-6} alkyl), -N(C_{0-6} alkyl)SO_2(C_{0-6} alkyl), -O(C_{0-6} alkyl), -S(C_{0-6} alkyl), -SO(C_{0-6} alkyl), -SO_2(C_{0-6} alkyl), -SO_2N(C_{0-6} alkyl)(C_{0-6} alkyl), -COO(C_{0-6} alkyl), -OCO(C_{0-6} alkyl), -CON(C_{0-6} alkyl)(C_{0-6} alkyl), -CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)(4-6-membered heterocyclyl), -SO_2(4-6-membered heterocyclyl), -COO(4-6-membered heterocyclyl), -OCO(4-6-membered heterocyclyl), -CON(C_{0-6} alkyl)(4-6-membered heterocyclyl), and -CO(4-6-membered heterocyclyl); wherein H in the alkyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_1-C_6 cyanoalkyl, -N(C_{0-6} alkyl)(C_{0-6} alkyl), -N(C_{0-6} alkyl)CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)CON(C_{0-6} alkyl), -N(C_{0-6} alkyl)SO_2(C_{0-6} alkyl), -O(C_{0-6} alkyl), -S(C_{0-6} alkyl), -SO(C_{0-6} alkyl), -SO_2(C_{0-6} alkyl), -SO_2N(C_{0-6} alkyl)(C_{0-6} alkyl), -COO(C_{0-6} alkyl), -OCO(C_{0-6} alkyl), -CON(C_{0-6} alkyl)(C_{0-6} alkyl), and -CO(C_{0-6} alkyl).

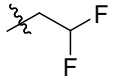
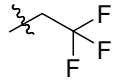
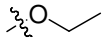
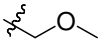
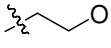
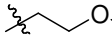
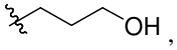
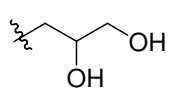
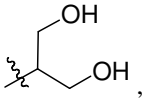
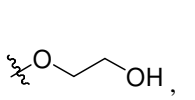
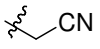
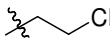
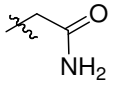
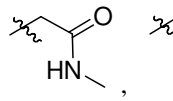
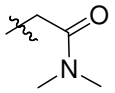
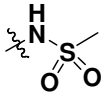
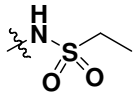
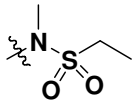
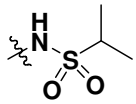
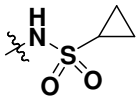
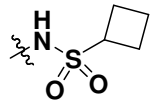
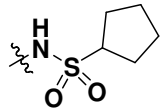
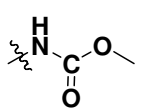
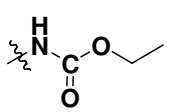
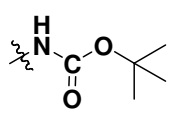
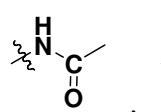
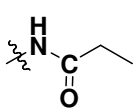
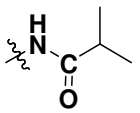
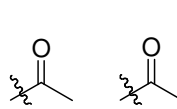
Specifically, in the definition of R^{Y41}, the 4-14-membered heterocyclyl is saturated or partially saturated heterocyclyl, for example,  , or ; and more specifically, R^{Y41} may be selected from the group consisting of:

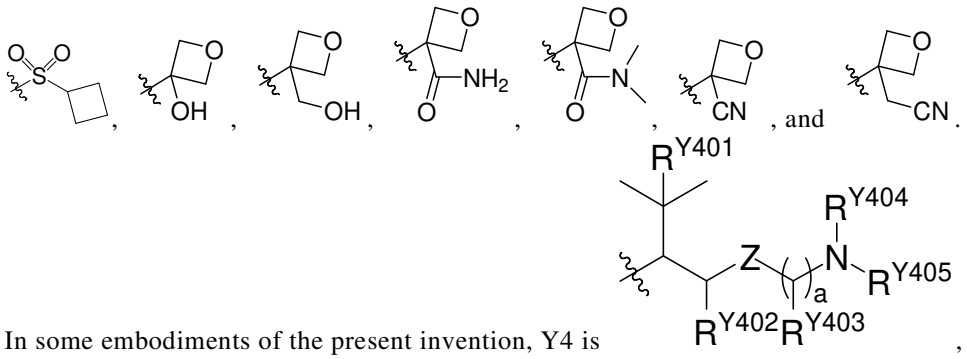
 ,

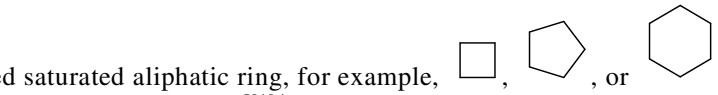
 ,

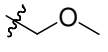
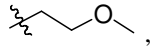
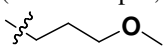
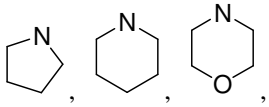
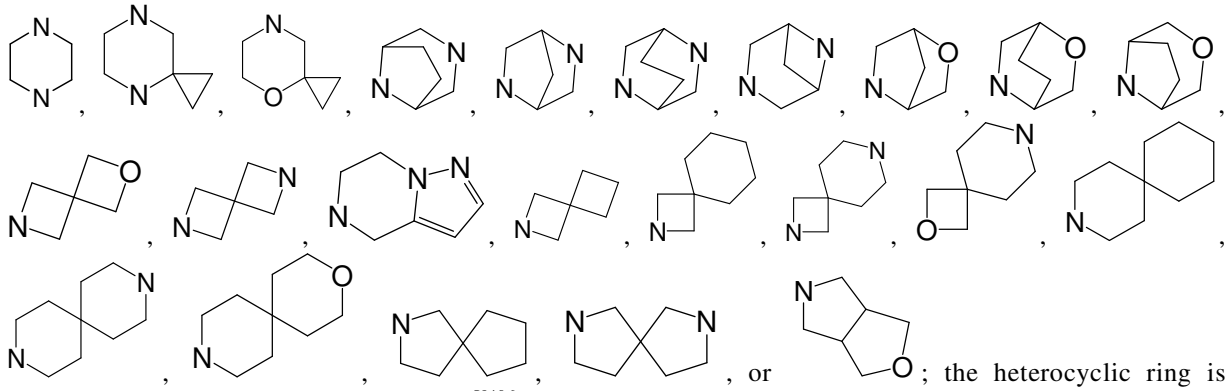
 ,

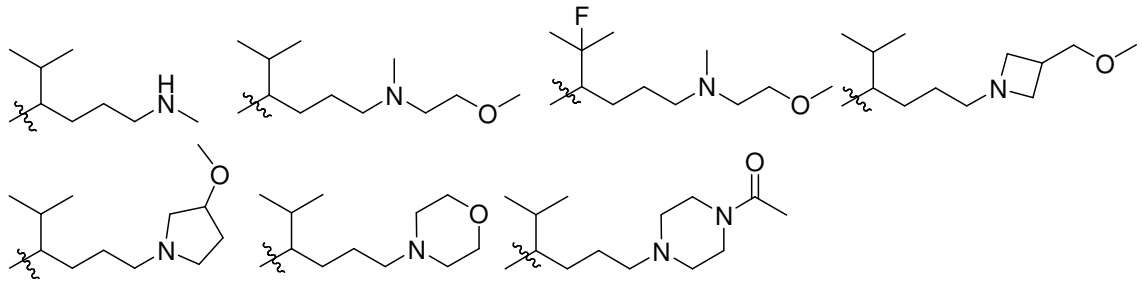

,

and .

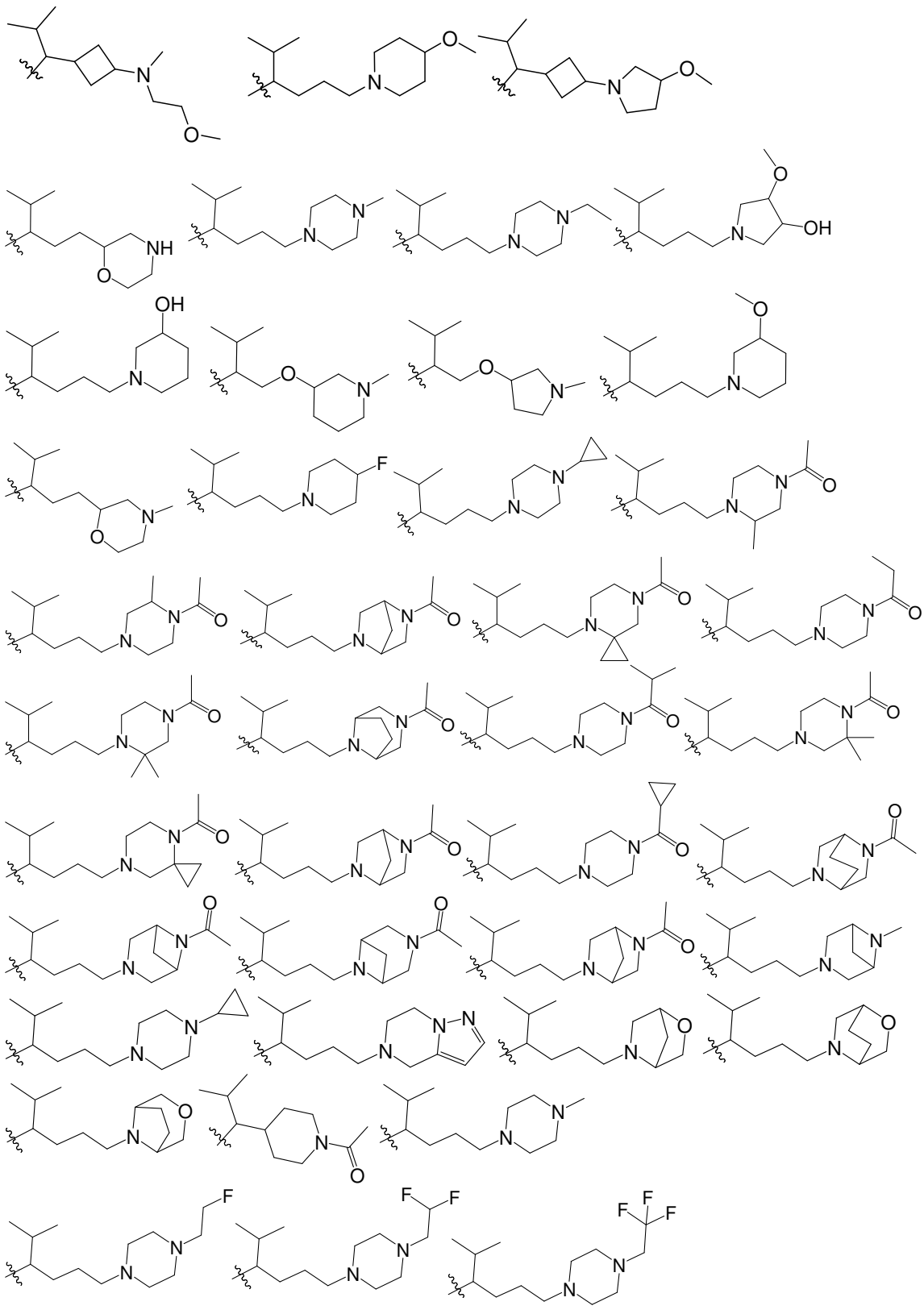
In some embodiments of the present invention, each R^{Y42} is independently selected from the group consisting of: H, halogen, , , , , , CF_3, CHF_2, CH_2F, ,  ,  , hydroxyl, ,  , ,  ,  ,  ,  ,  ,  ,  , cyano,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

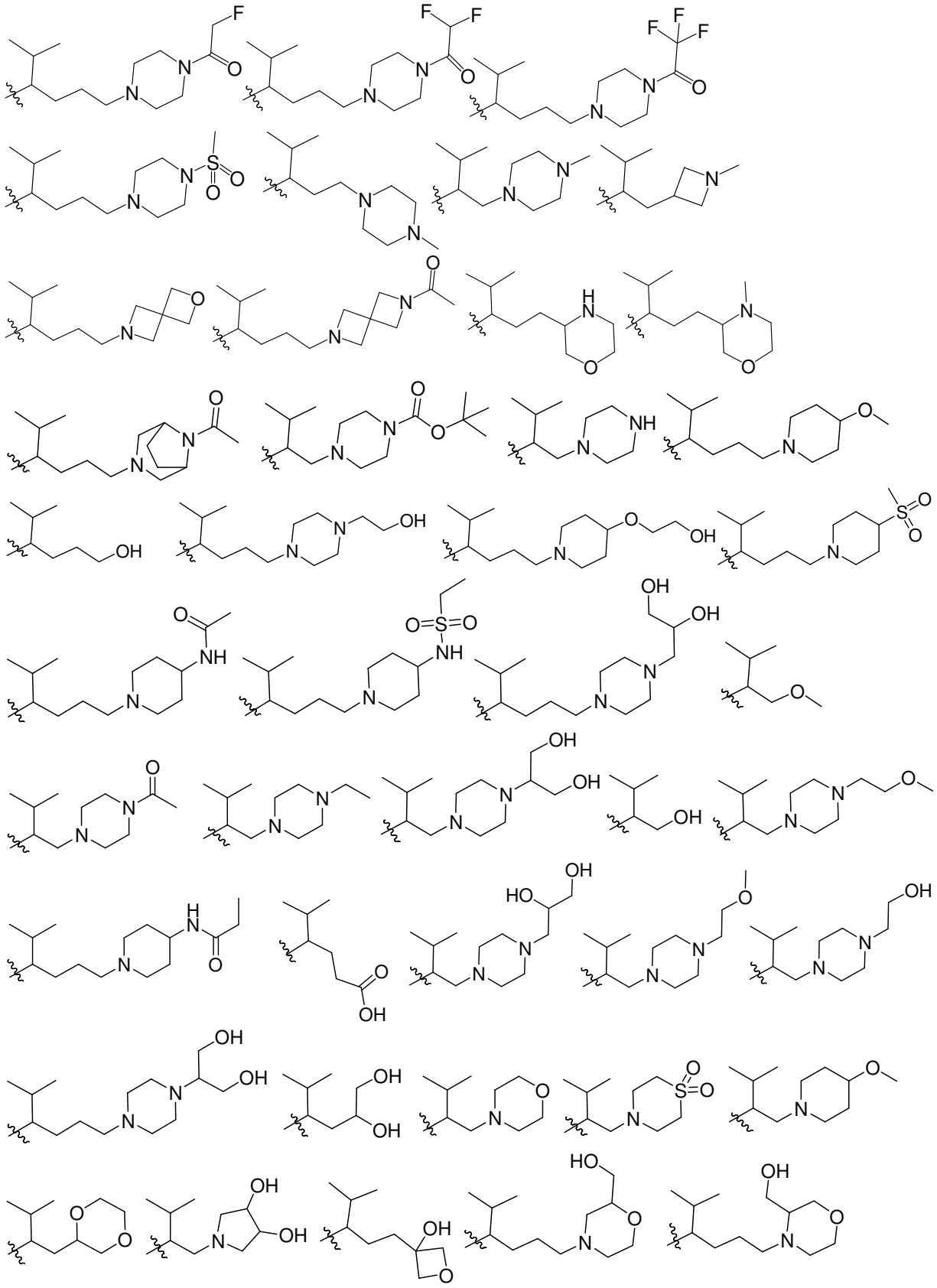


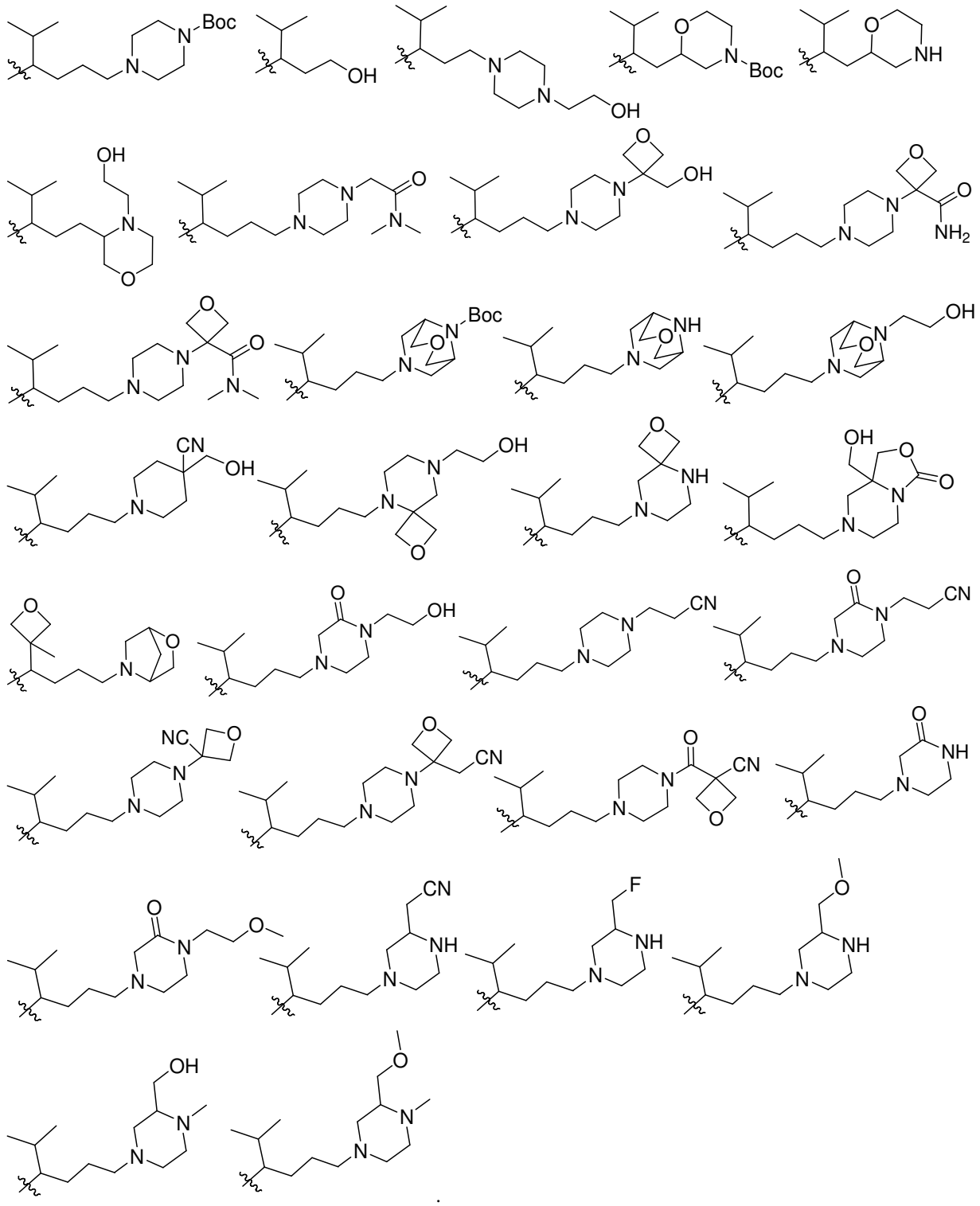
In some embodiments of the present invention, Y4 is , wherein,
R^{Y401} is selected from the group consisting of: H, halogen (for example, F), C_1-C_3 alkyl, and C_1-C_3 halogenated alkyl;
R^{Y402} and R^{Y403} are independently selected from the group consisting of: H, halogen (for example, F), hydroxyl, amino, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, and -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), wherein the alkyl or cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y402} and R^{Y403}, together with the carbon atom attached thereto, form an aliphatic ring or a heterocyclic ring, wherein the aliphatic ring or heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, and halogenated C_1-C_6 alkyl;
R^{Y404} and R^{Y405} are independently selected from the group consisting of: H and C_1-C_6 alkyl, wherein the alkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y404} and R^{Y405}, together with the nitrogen atom attached thereto, form a heterocyclic ring, or, R^{Y402} and R^{Y404}, together with the nitrogen or nitrogen atom attached thereto, form a heterocyclic ring, R^{Y403} and R^{Y404}, together with the carbon or nitrogen atom attached thereto, form a heterocyclic ring, wherein the heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in the $C_{0\text{-}10}$ alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl);
Z is selected from the group consisting of: C_0-C_6 alkylene, -(C_0-C_3 alkylene)-O-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-S-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-C(O)NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NHC(O)-(C_0-C_3 alkylene)-; and
a is 0 or 1.
In some embodiments of the present invention, R^{Y401} is selected from the group consisting of: H and halogen (for example, F).
In some embodiments of the present invention, R^{Y401} is H.
In some embodiments of the present invention, R^{Y401} is F.
In some embodiments of the present invention, R^{Y402} and R^{Y403} are independently selected from the group consisting of: H, halogen (for example, F), hydroxyl, amino, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, hydroxyl-substituted C_1-C_3 alkyl, alkoxy-substituted C_1-C_6 alkyl, amino-substituted C_1-C_3 alkyl, and alkylamino-substituted C_1-C_6 alkyl.
In some embodiments of the present invention, R^{Y402} and R^{Y403} are both H.
In some embodiments of the present invention, R^{Y402} and R^{Y403}, together with the carbon atom attach thereto, form a four- to six-membered saturated aliphatic ring, for example,  .
In some embodiments of the present invention, R^{Y404} is selected from the group consisting of: H and C_1-C_6 alkyl (for example, methyl).

In some embodiments of the present invention, R^{Y404} is H.
In some embodiments of the present invention, R^{Y405} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, alkoxy-substituted C_1-C_6 alkyl, amino-substituted C_1-C_6 alkyl, and alkylamino-substituted C_1-C_6 alkyl.
In some embodiments of the present invention, R^{Y405} is selected from the group consisting of: C_1-C_6 alkyl (for example, methyl), and alkoxy-substituted C_1-C_6 alkyl (for example,  ,  , or ).
In some embodiments of the present invention, R^{Y404} and R^{Y405}, together with the nitrogen atom attached thereto, form a four- to twelve-membered nitrogenous heterocyclic ring, for example,  ,  , , , ; the heterocyclic ring is optionally substituted with one or more R^{Y406} groups;
R^{Y406} is selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in the $C_{0\text{-}10}$ alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl).
In some embodiments of the present invention, R^{Y406} is selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_1-C_6 alkylamino, C_1-C_6 alkylaminoalkyl, C_3-C_6 cycloalkyl, -CO($C_{0\text{-}6}$ alkyl), -CO(C_3-C_6 cycloalkyl), -CO(halogenated $C_{0\text{-}6}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), and -SO_2(halogenated $C_{0\text{-}10}$ alkyl).
In some embodiments of the present invention, a is 1.
In some embodiments of the present invention, Z is a single bond, methylene or O.
In some embodiments of the present invention, a is 0, and Z is O.
In some embodiments of the present invention, a is 1, and Z is methylene.
In some embodiments of the present invention, Y4 is selected from the group consisting of:

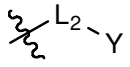


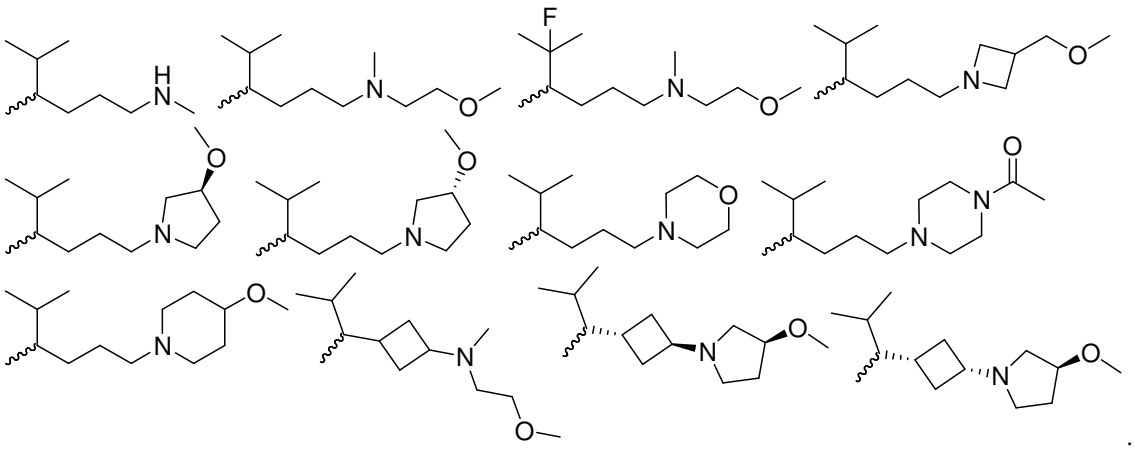






In some embodiments of the present invention, L_2 is a single bond, and Y is Y4.

In some embodiments of the present invention, the  moiety is selected from the group consisting of:



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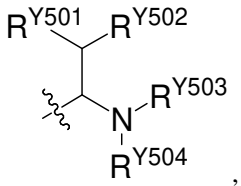


In some embodiments of the present invention, Y5 is , wherein R^{Y501} and R^{Y502} are independently selected from the group consisting of: H, halogen (for example, F), hydroxyl, amino, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, and -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), wherein the alkyl or cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y501} and R^{Y502}, together with the carbon atom attached thereto, form an aliphatic ring or a heterocyclic ring, wherein the aliphatic ring or heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, and halogenated C_1-C_6 alkyl;

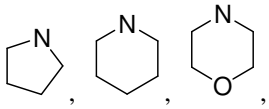
R^{Y503} and R^{Y504} are independently selected from the group consisting of: H and C_1-C_6 alkyl, wherein said alkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y503} and R^{Y504}, together with the nitrogen atom attached thereto, form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in said $C_{0\text{-}10}$ alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl).

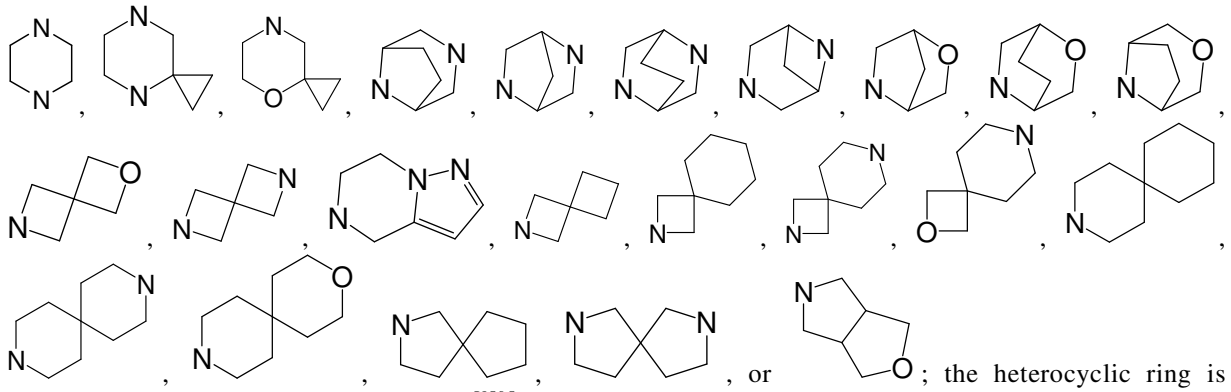
In some embodiments of the present invention, R^{Y501} and R^{Y502} are independently selected from the group consisting of: C_1-C_3 alkyl, and halogenated C_1-C_3 alkyl.

In some embodiments of the present invention, R^{Y501} and R^{Y502}, together with the carbon atom attached thereto, form C_3-C_6 cycloalkyl, and the C_3-C_6 cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_3 alkoxy, and C_1-C_3 alkylamino.

In some embodiments of the present invention, R^{Y503} is H.

In some embodiments of the present invention, R^{Y503} is C_1-C_3 alkyl.

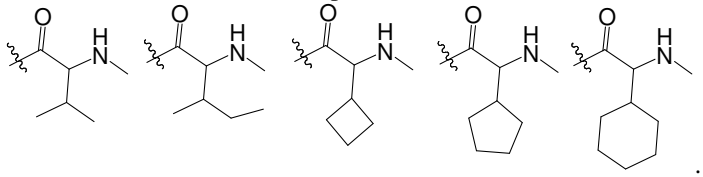
In some embodiments of the present invention, R^{Y503} and R^{Y504}, together with the nitrogen atom attached thereto, form a four- to twelve-membered nitrogenous heterocyclic ring, for example,  ,


; the heterocyclic ring is optionally substituted with one or more R^{Y505} groups;

R^{Y505} is selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in the $C_{0\text{-}10}$ alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl).

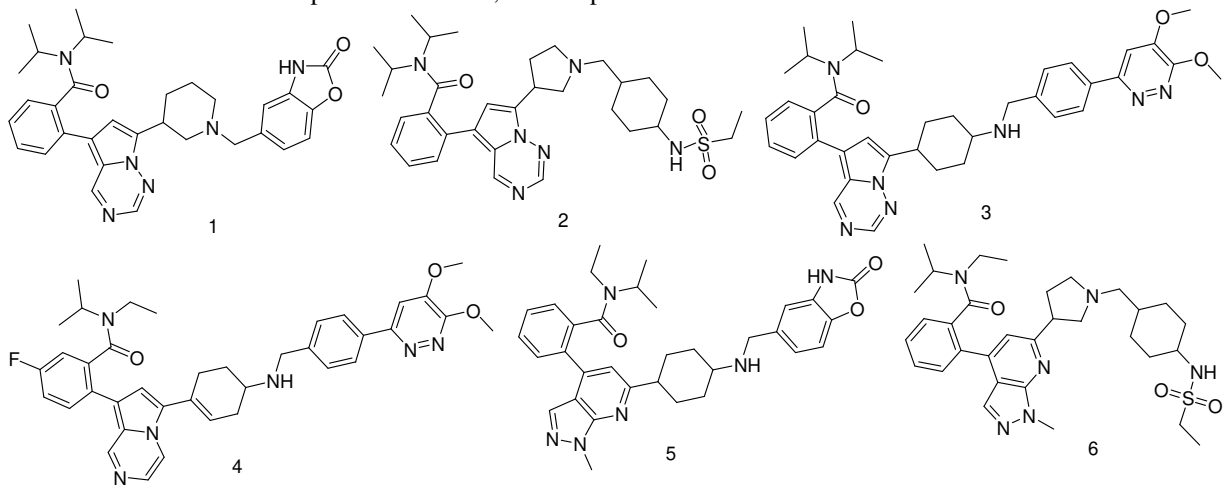
In some embodiments of the present invention, R^{Y505} is selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_1-C_6 alkylamino, C_1-C_6 alkylaminoalkyl, C_3-C_6 cycloalkyl, -CO($C_{0\text{-}6}$ alkyl), -CO(C_3-C_6 cycloalkyl), -CO(halogenated $C_{0\text{-}6}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), and -SO_2(halogenated $C_{0\text{-}10}$ alkyl).

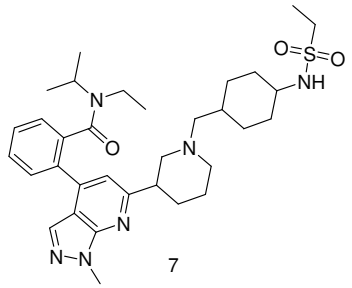
In some embodiments of the present invention, Y5 is selected from the group consisting of:


.

In some embodiments of the present invention, L_2 is C(O), and Y is Y5.

In some embodiments of the present invention, the compound has a structure as follows:





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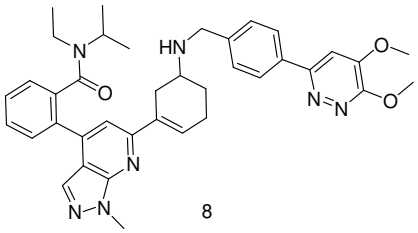

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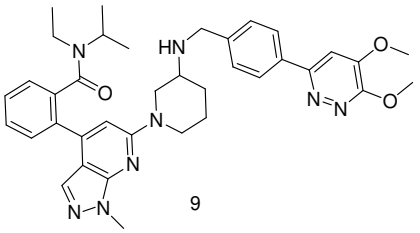

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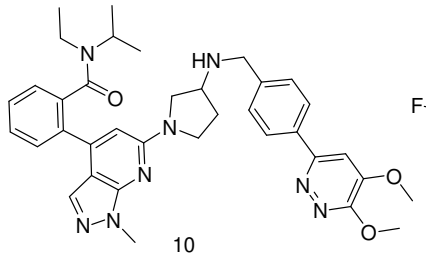

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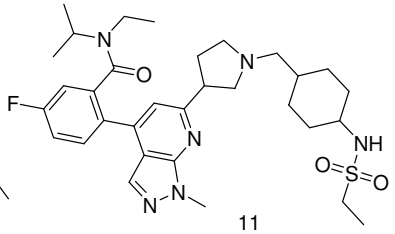

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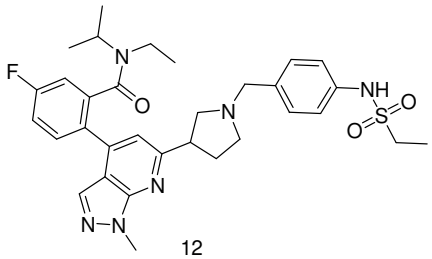

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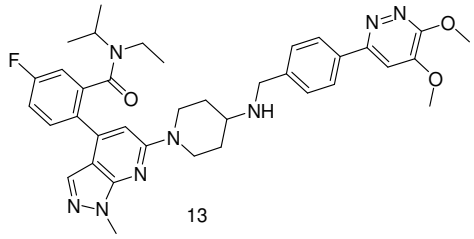

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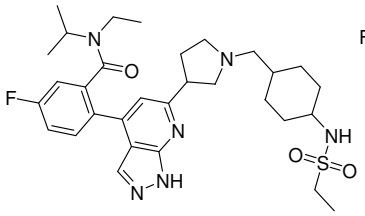

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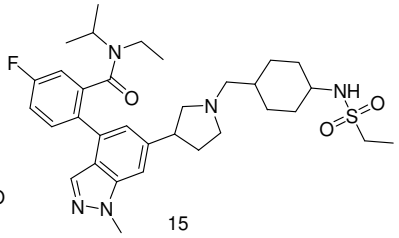

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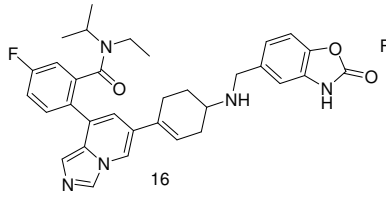

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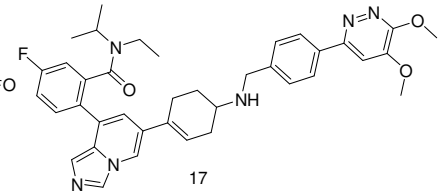

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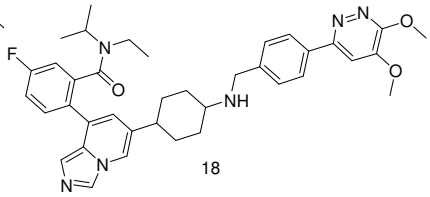

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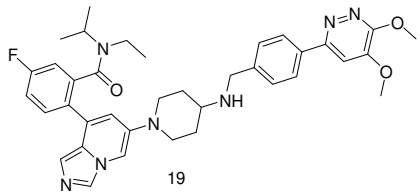

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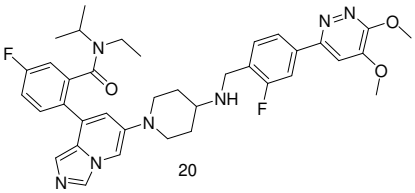

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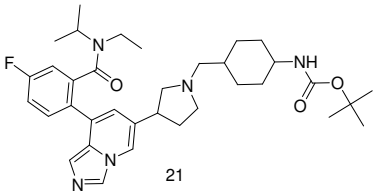

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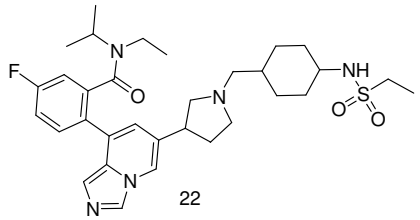

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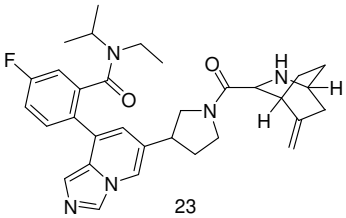

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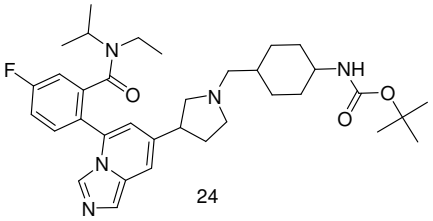

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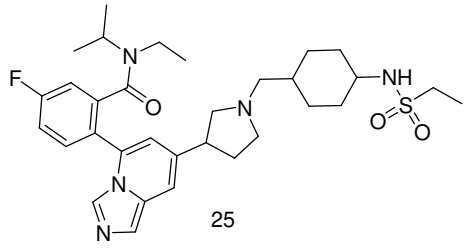

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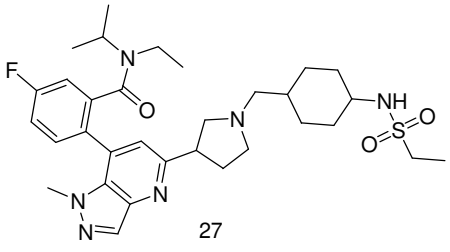

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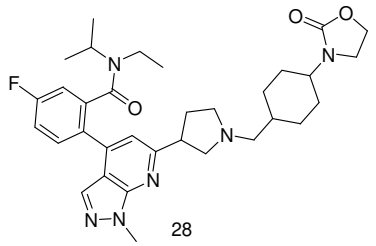

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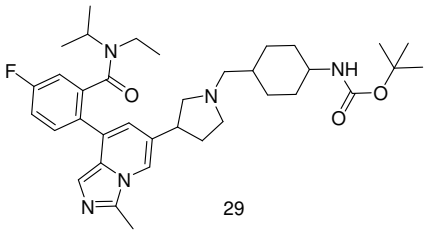

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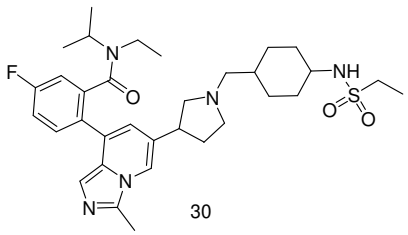

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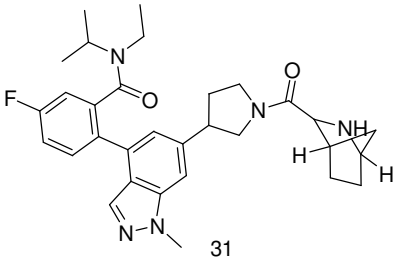

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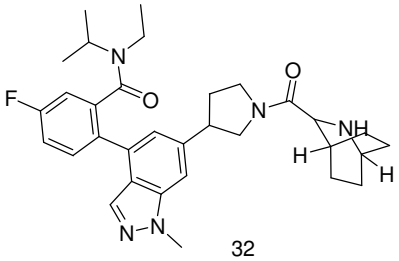

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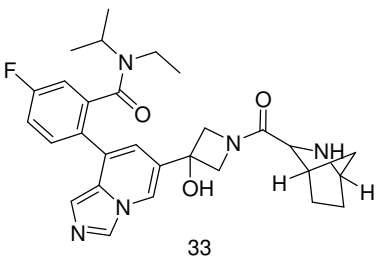

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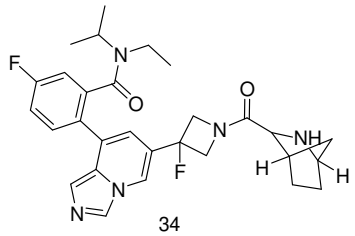

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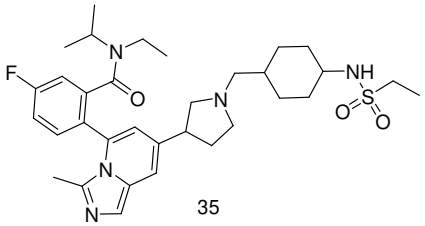

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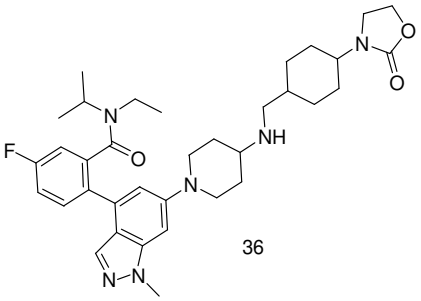

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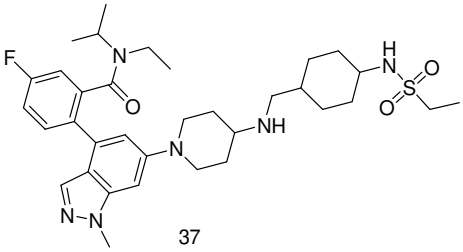

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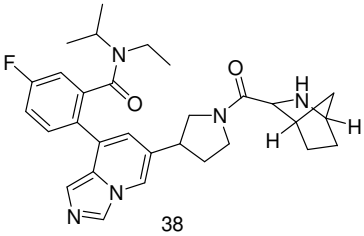

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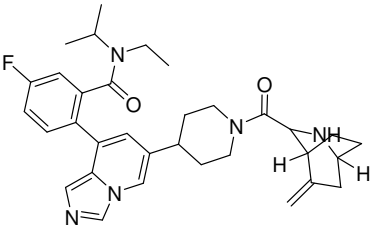

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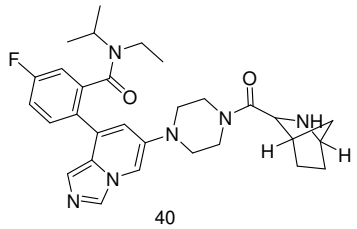

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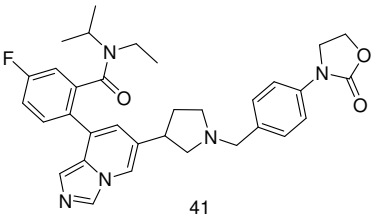

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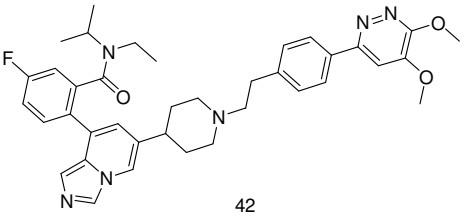

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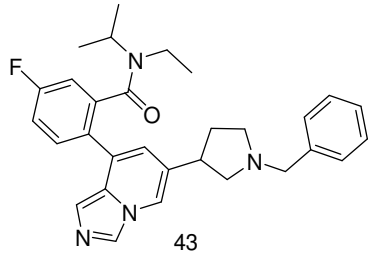

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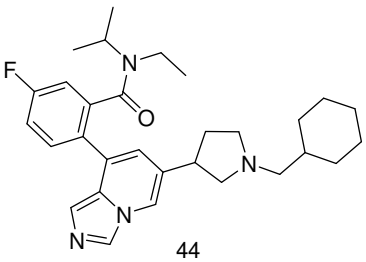

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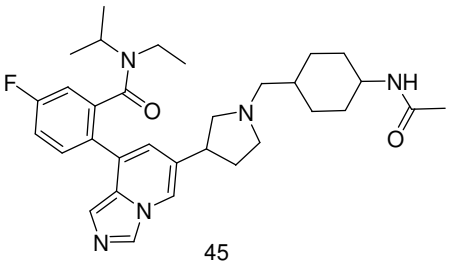

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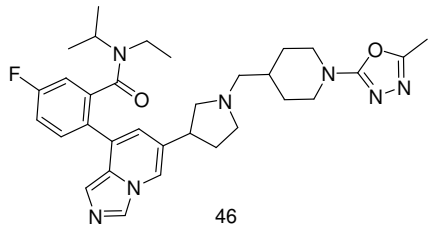

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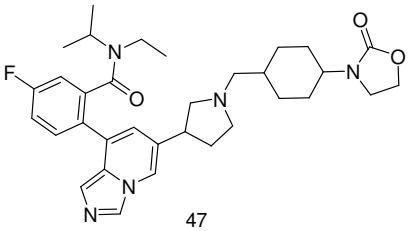

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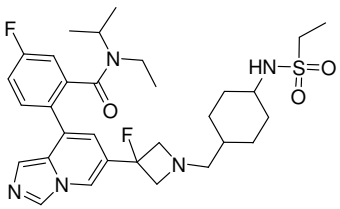

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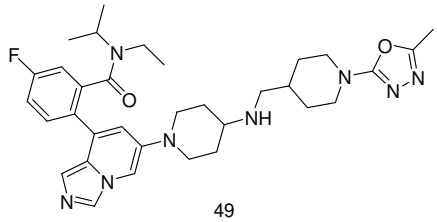

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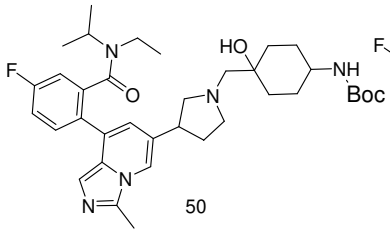

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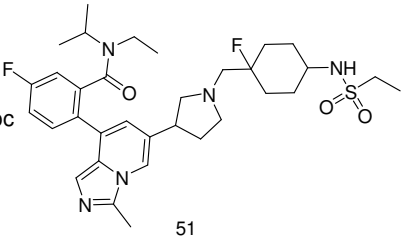

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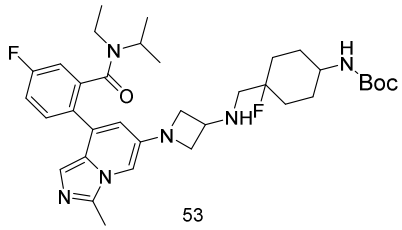

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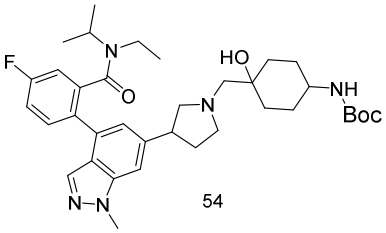

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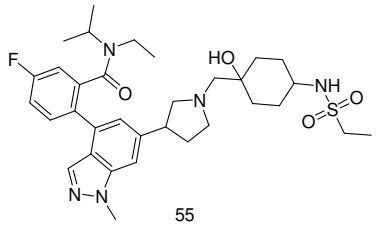

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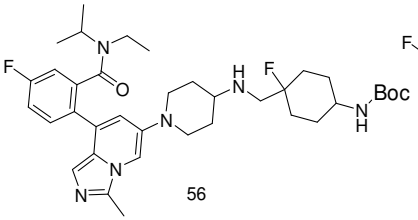

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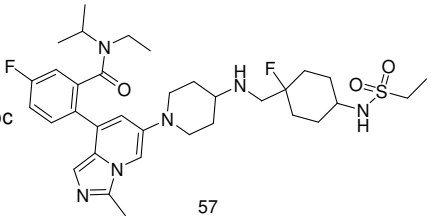

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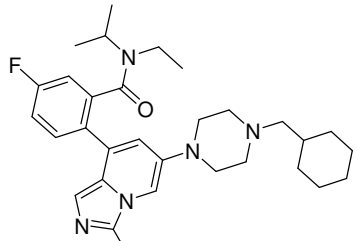

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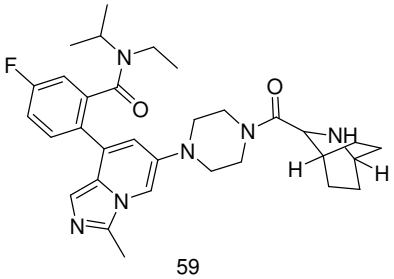

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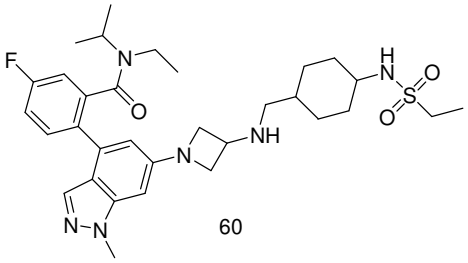

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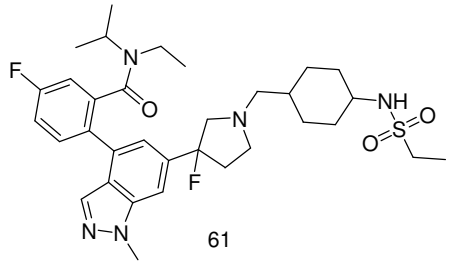

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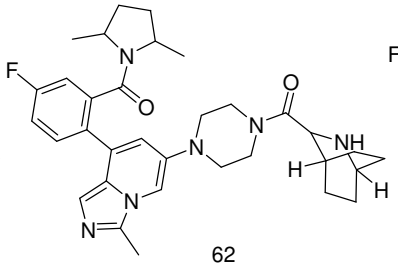

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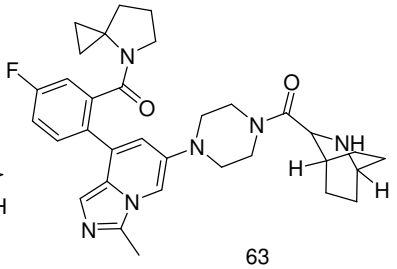

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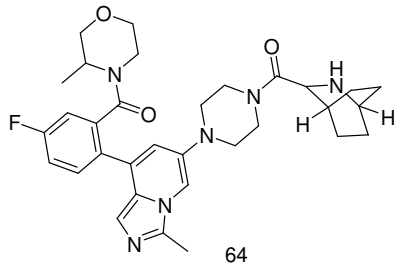

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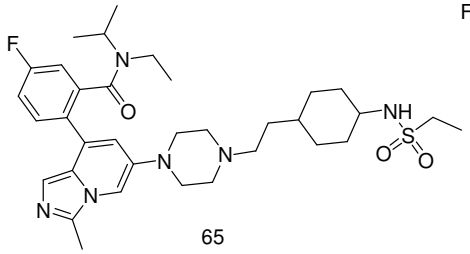

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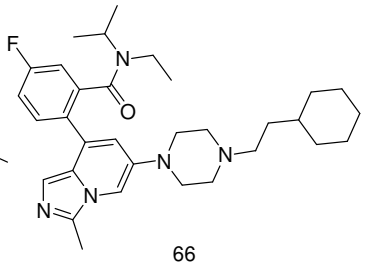

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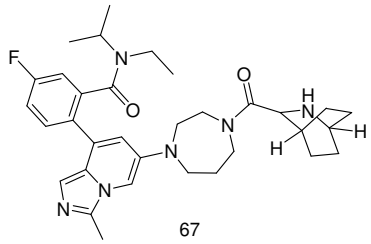

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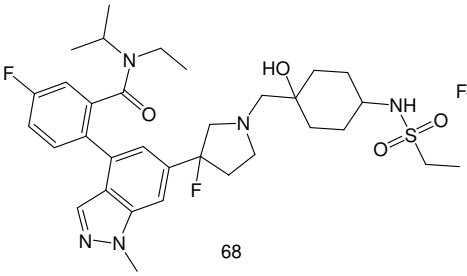

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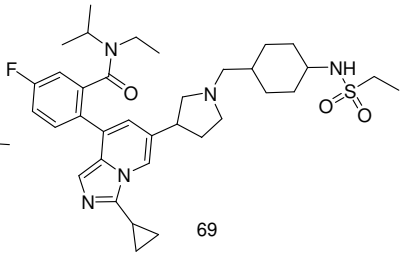

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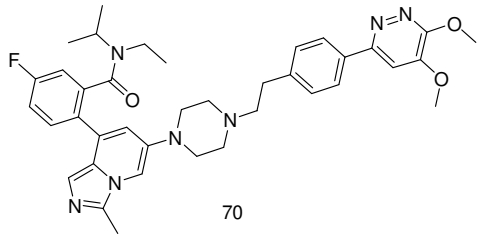

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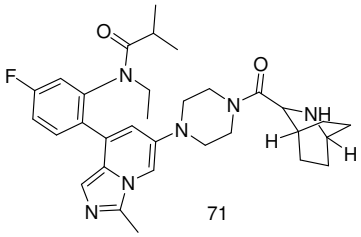

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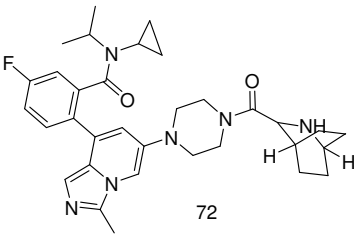

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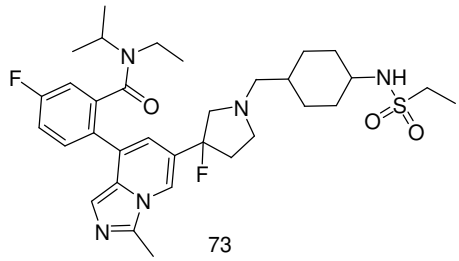

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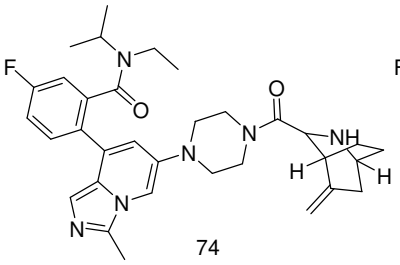

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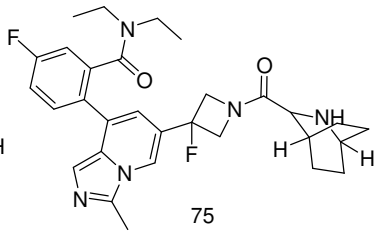

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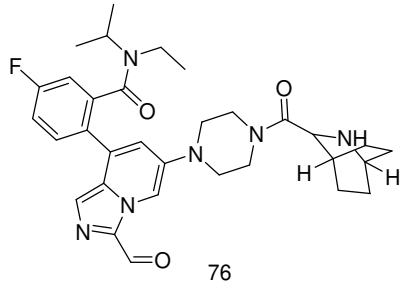

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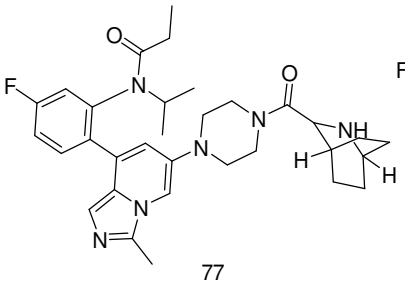

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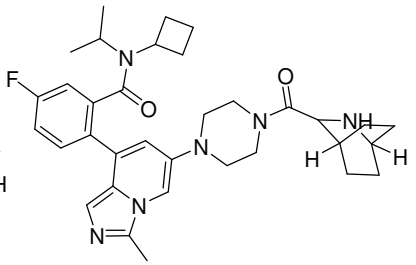

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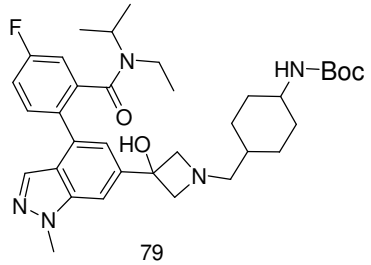

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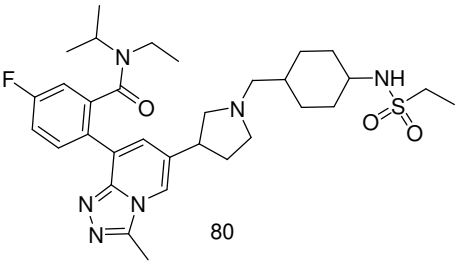

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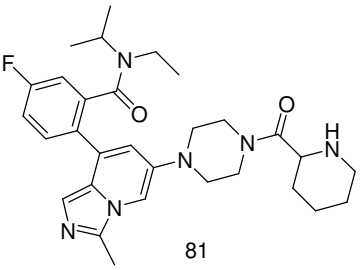

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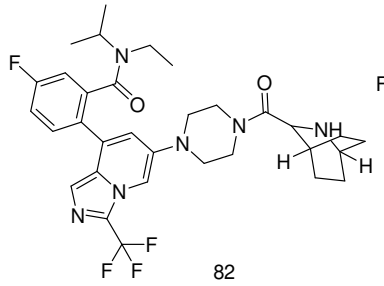

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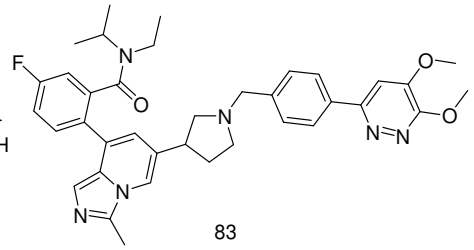

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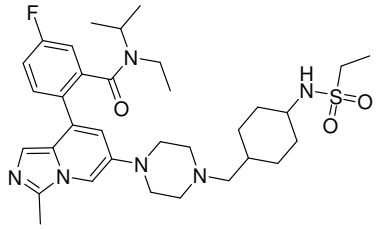

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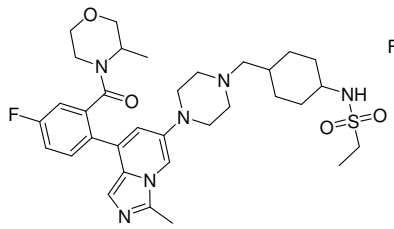

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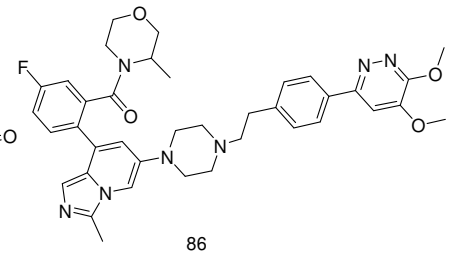

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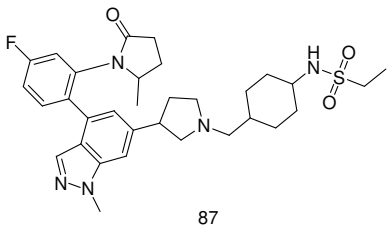

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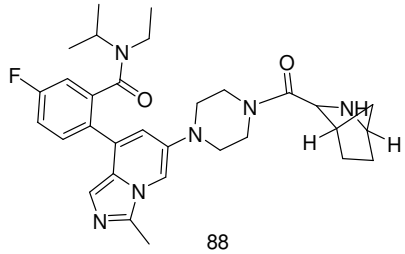

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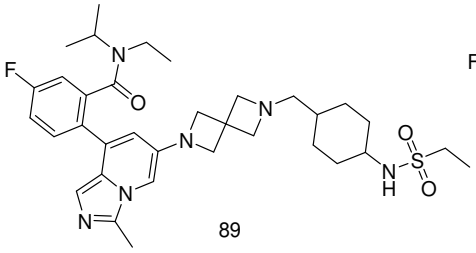

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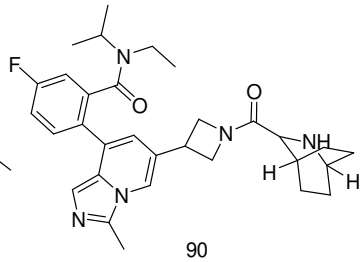

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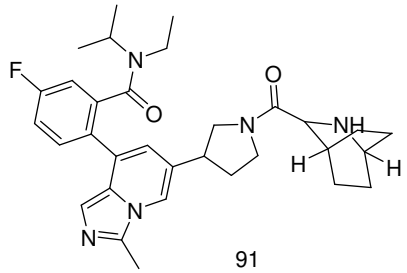

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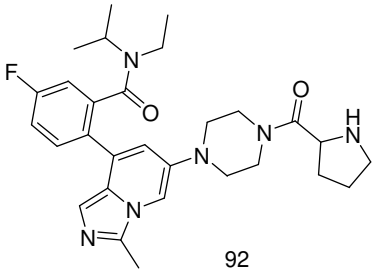

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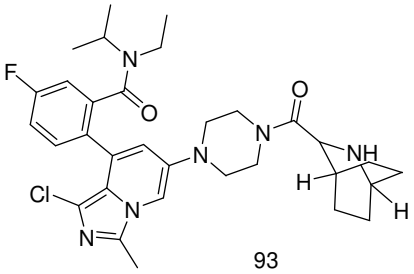

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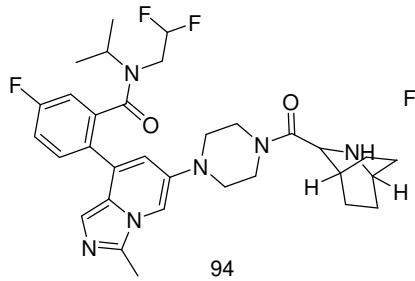

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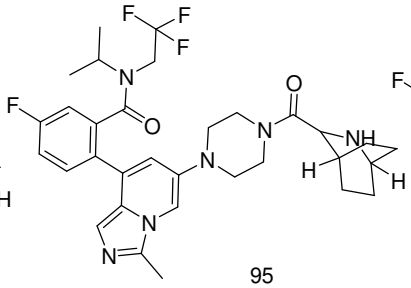

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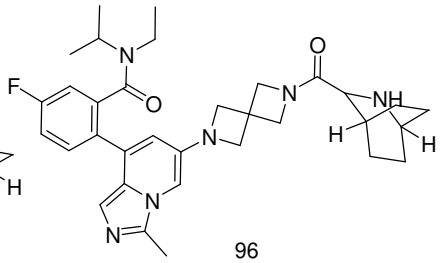

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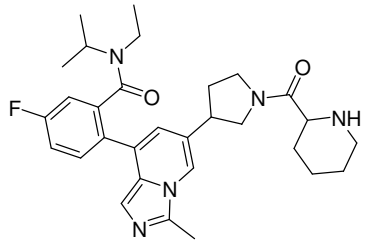

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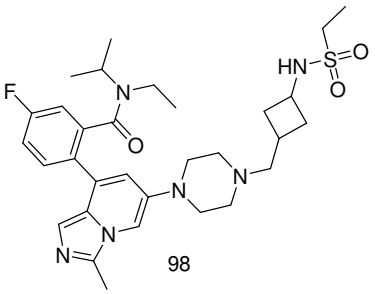

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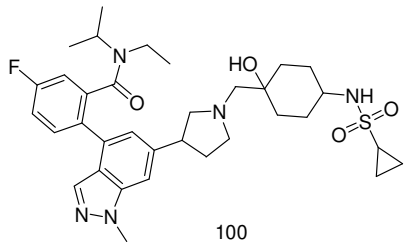

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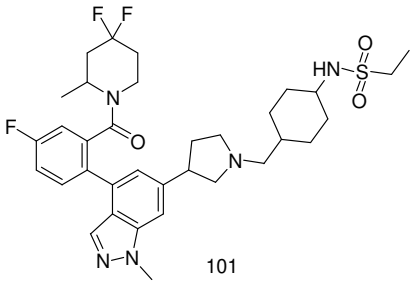

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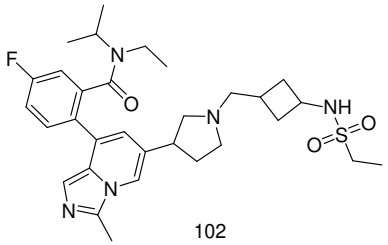

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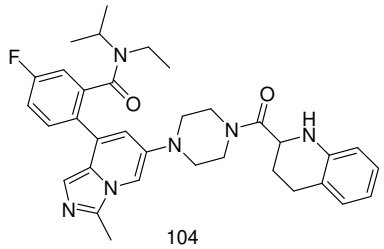

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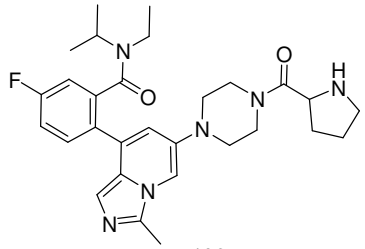

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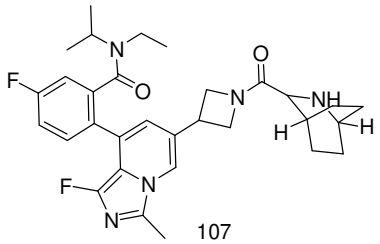

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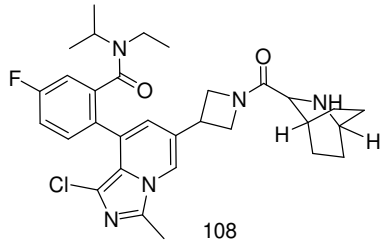

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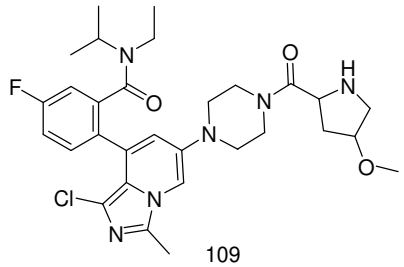

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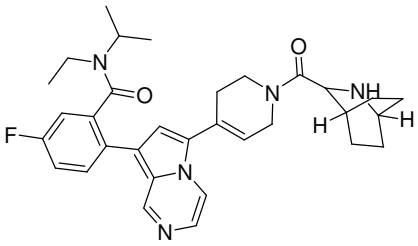

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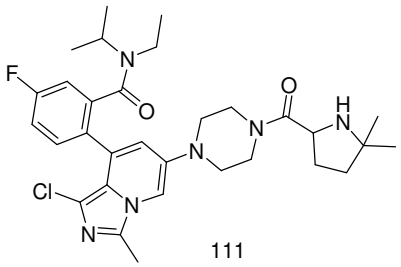

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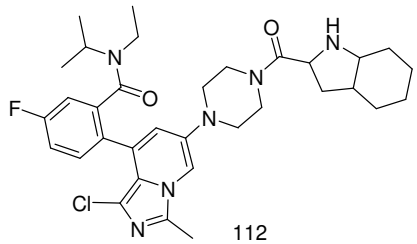

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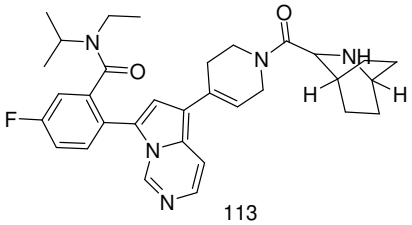

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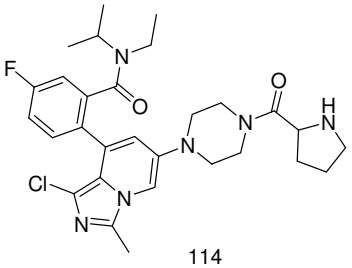

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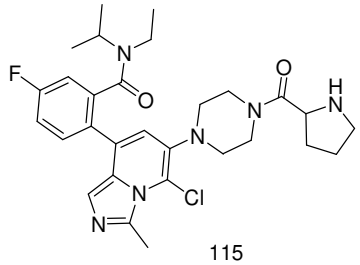

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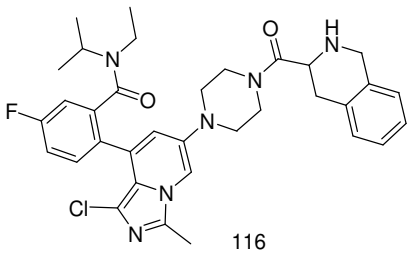

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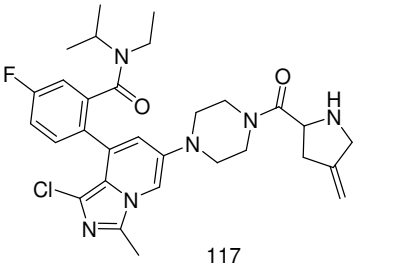

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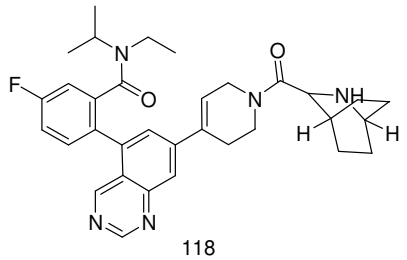

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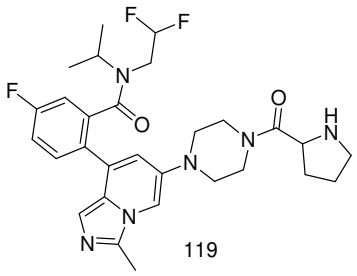

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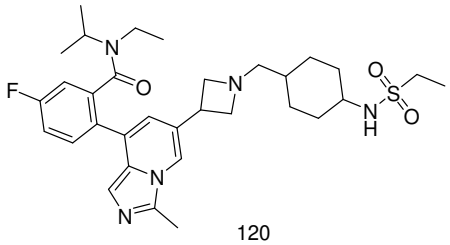

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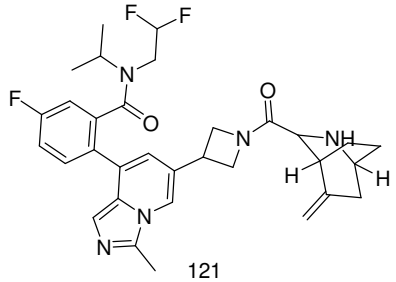

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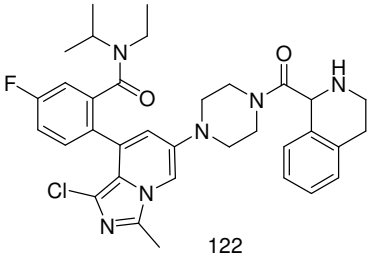

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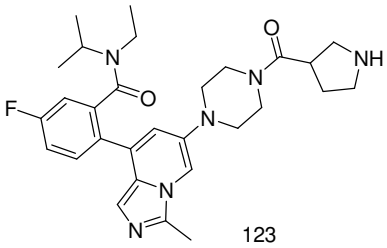

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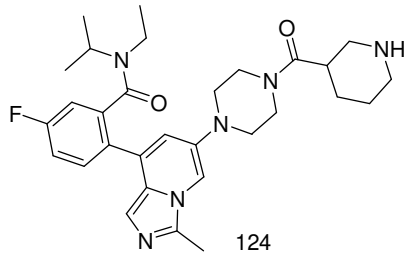

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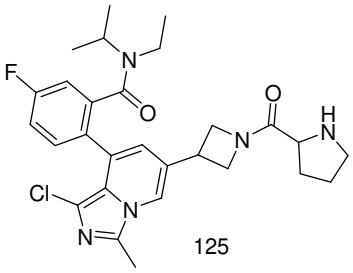

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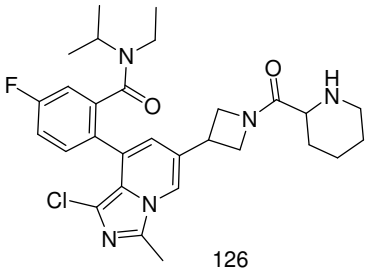

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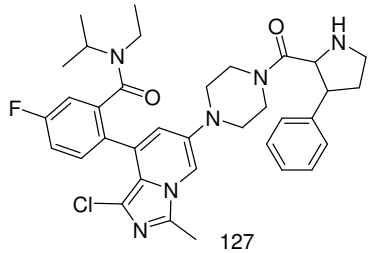

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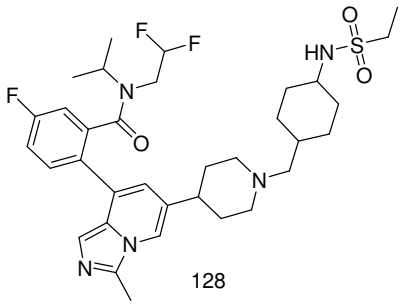

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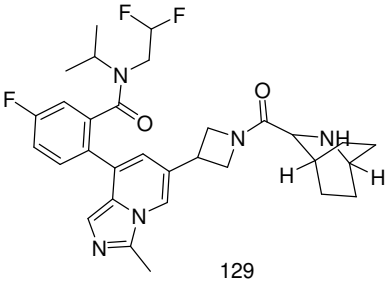

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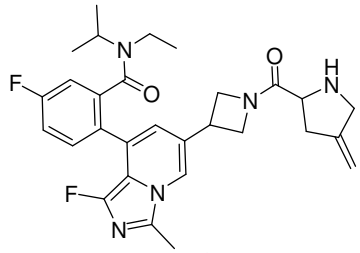

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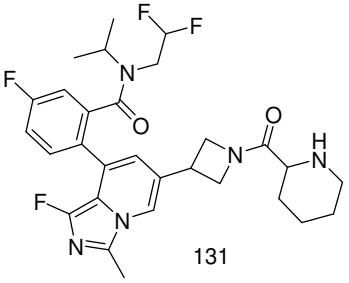

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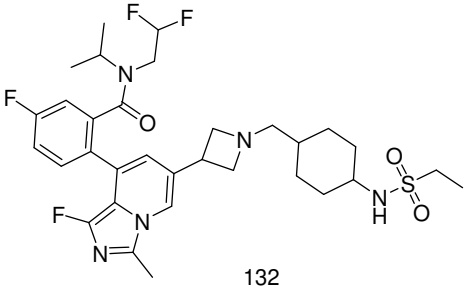

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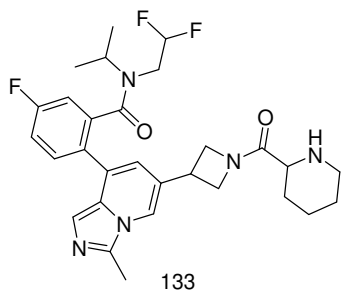

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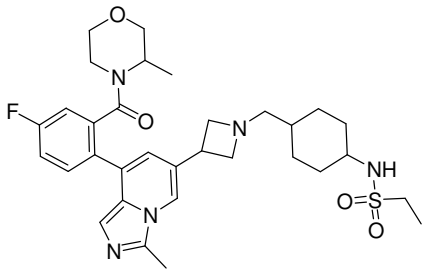

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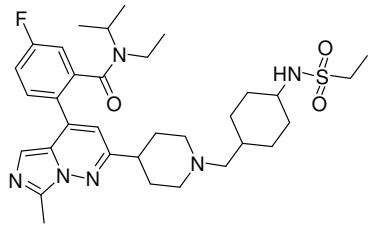

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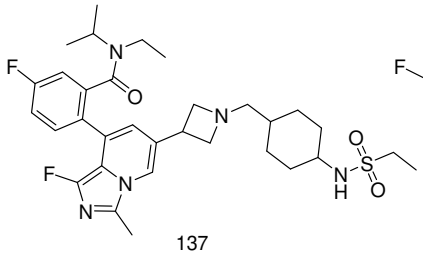

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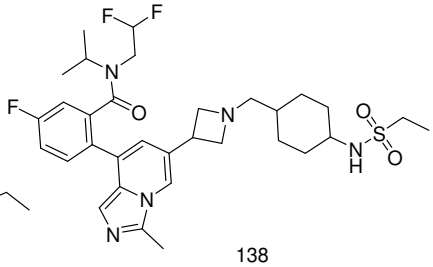

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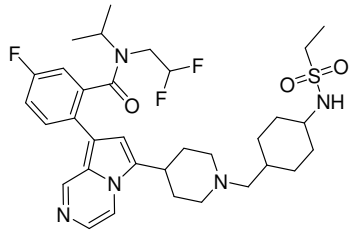

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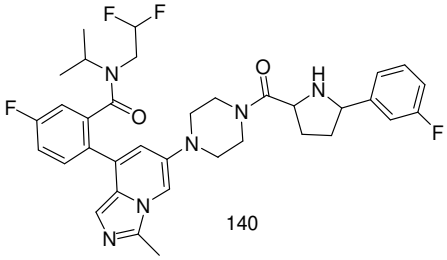

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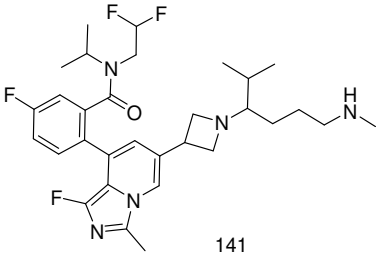

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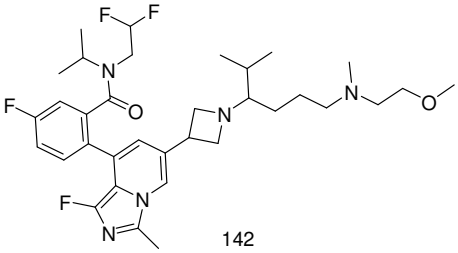

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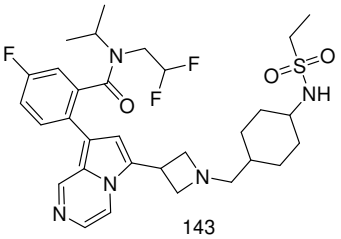

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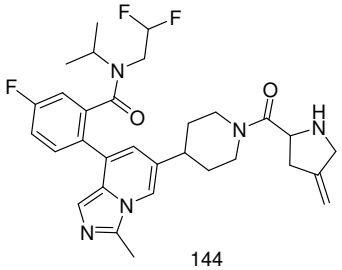

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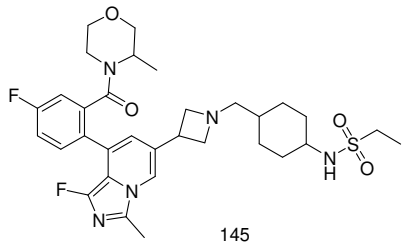

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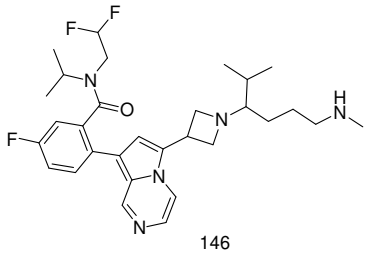

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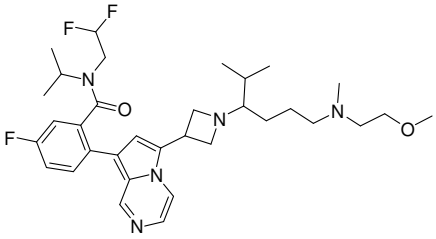

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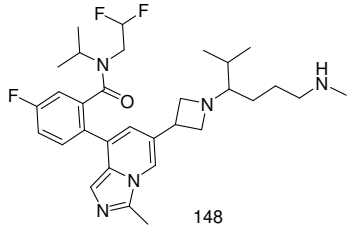

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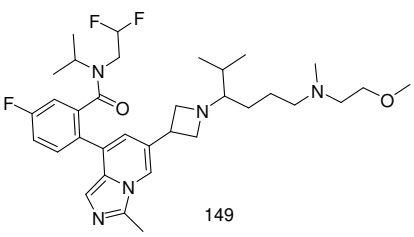

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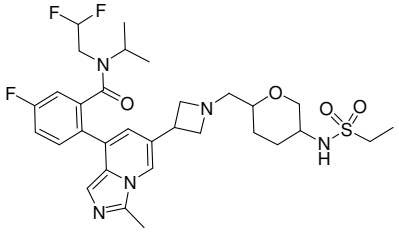

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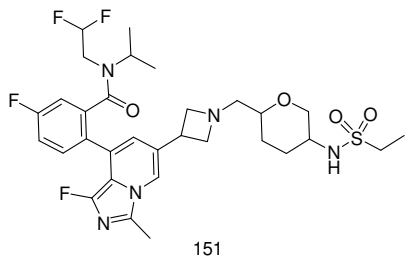

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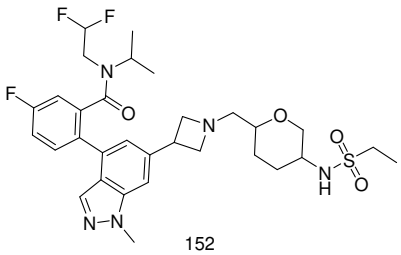

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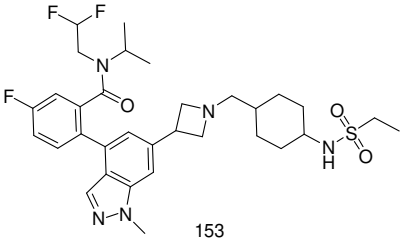

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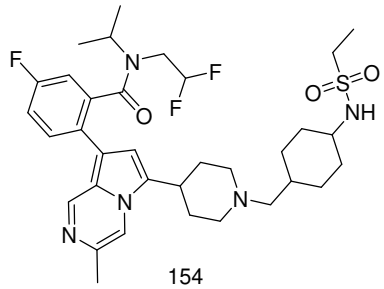

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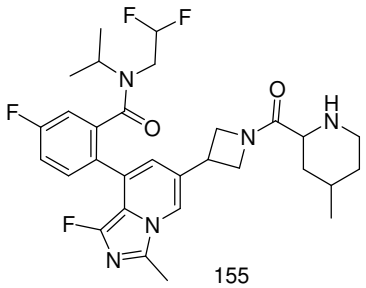

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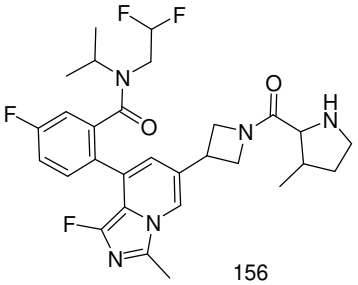

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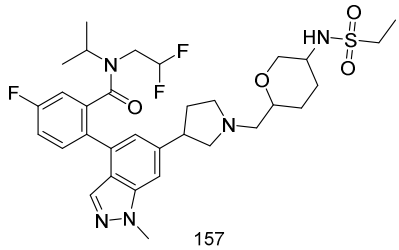

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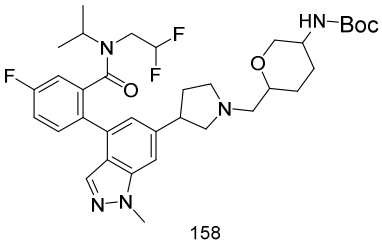

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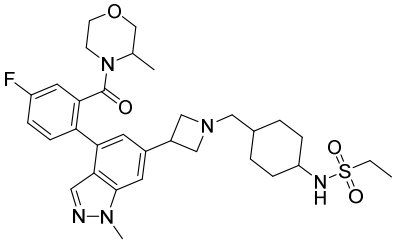

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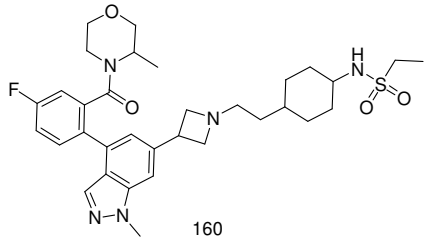

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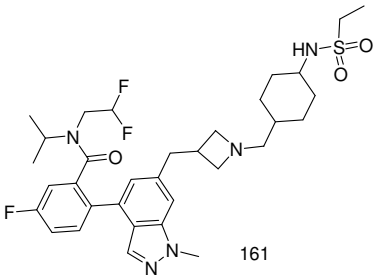

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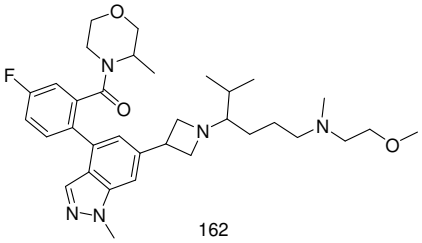

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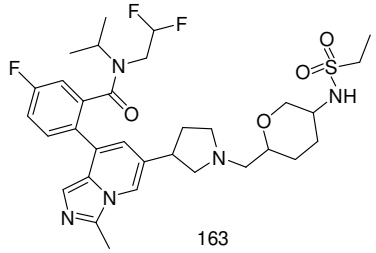

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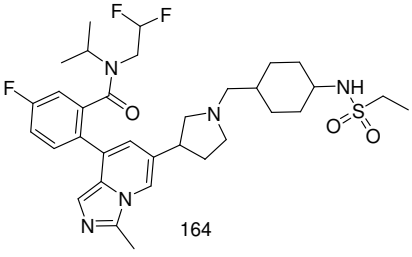

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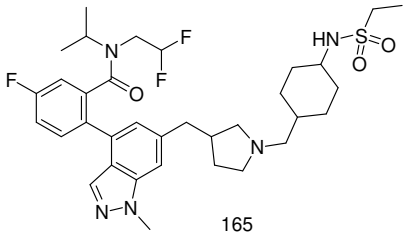

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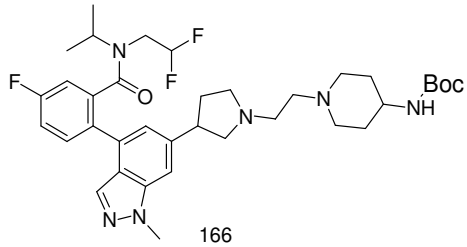

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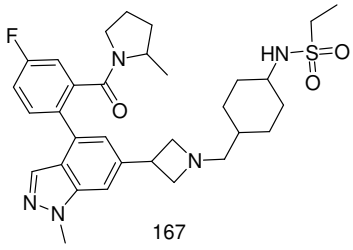

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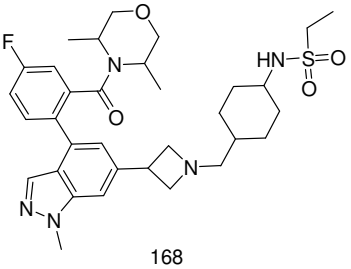

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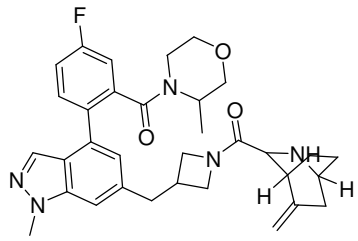

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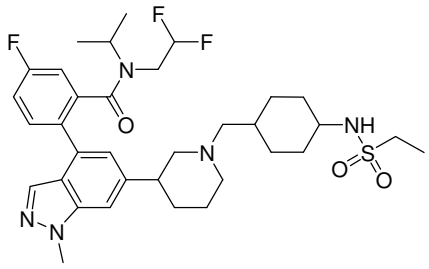

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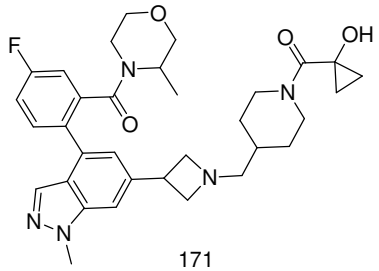

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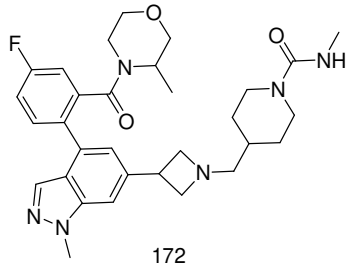

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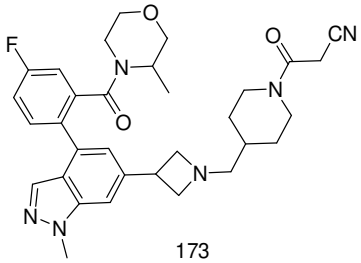

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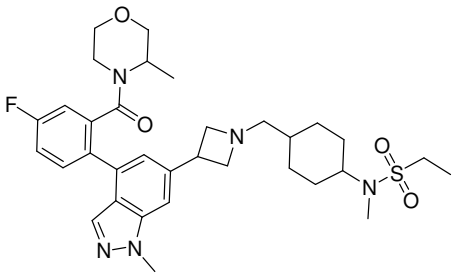

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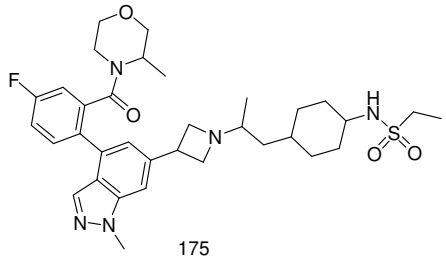

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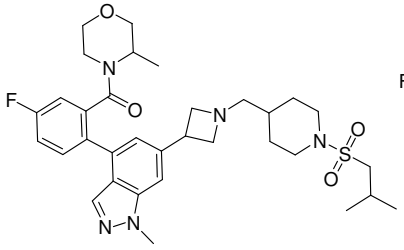

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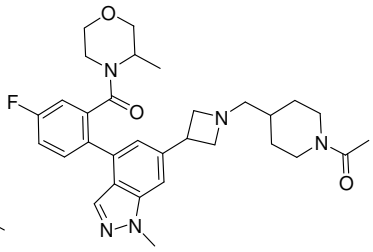

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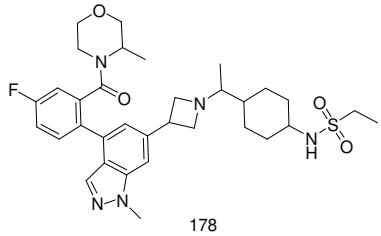

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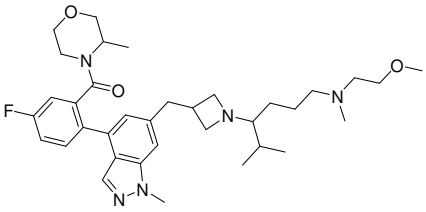

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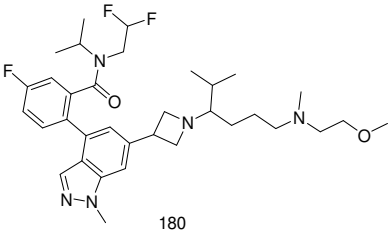

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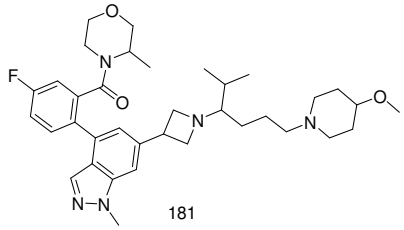

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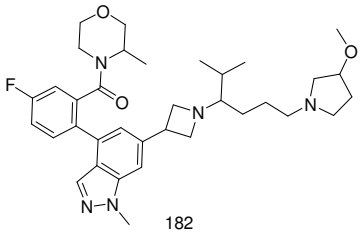

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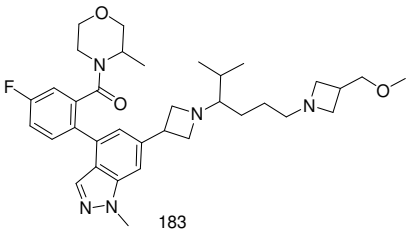

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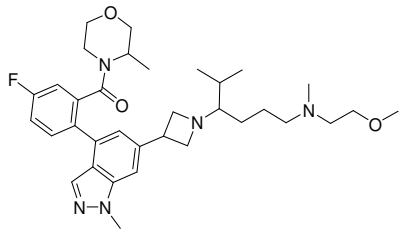

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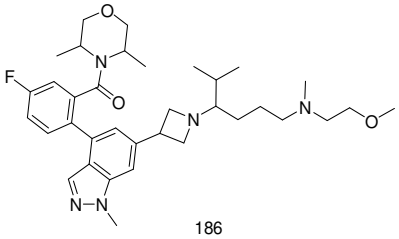

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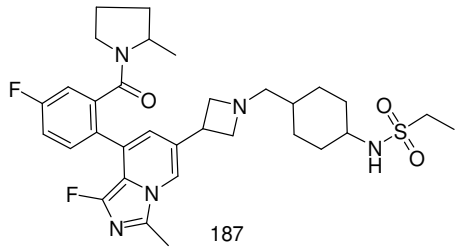

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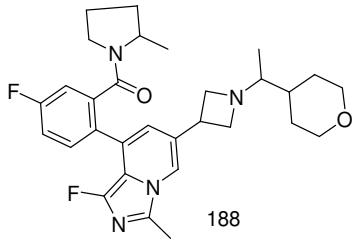

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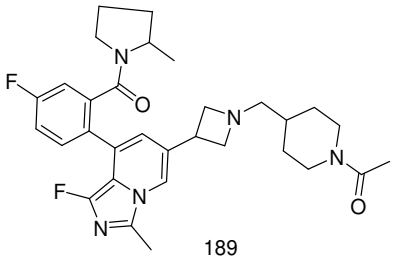

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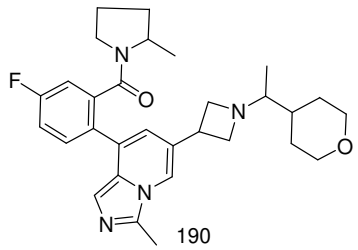

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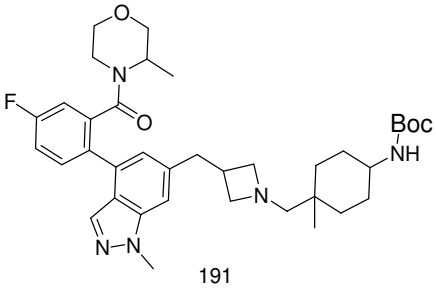

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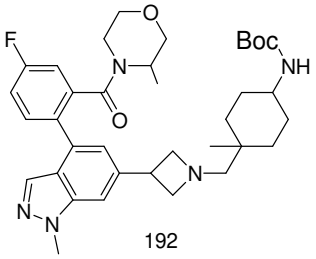

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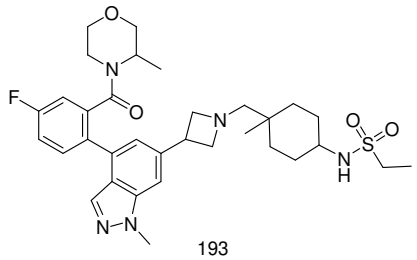

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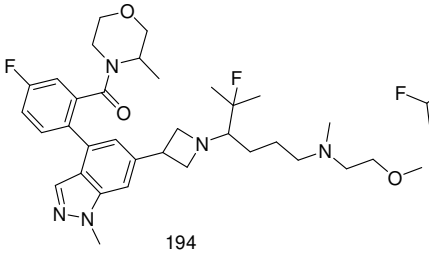

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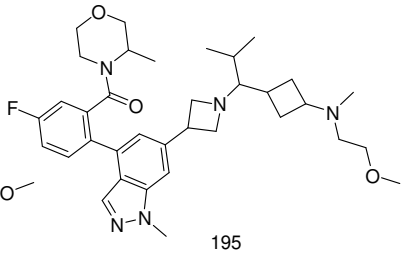

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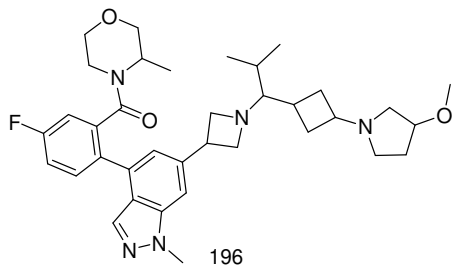

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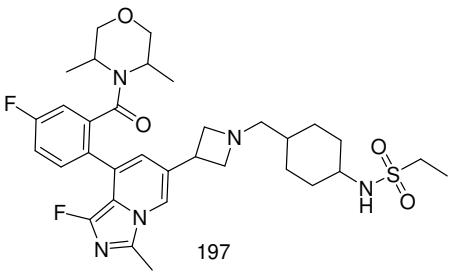

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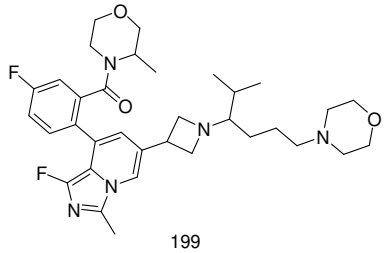

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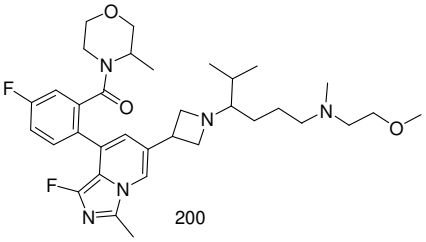

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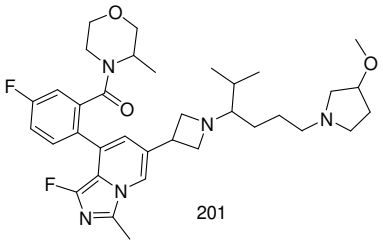

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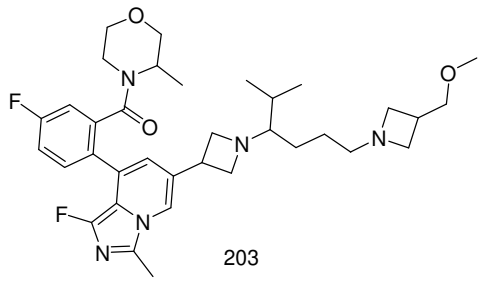

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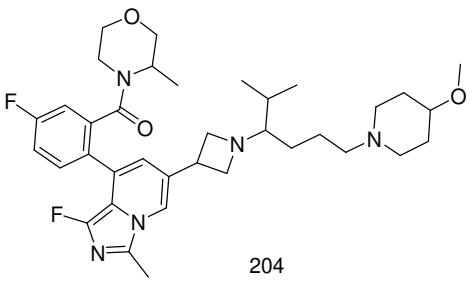

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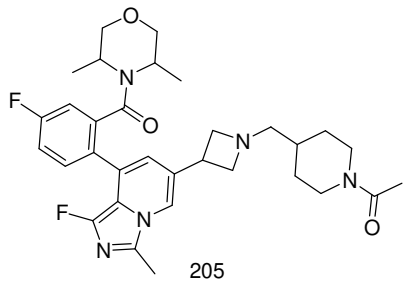

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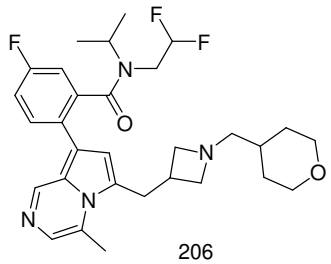

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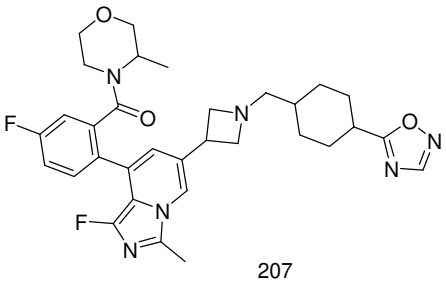

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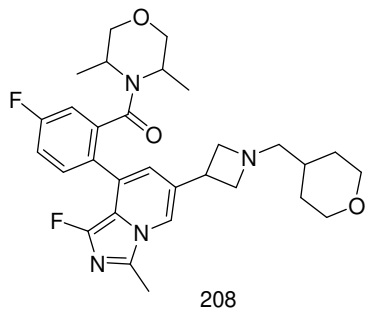

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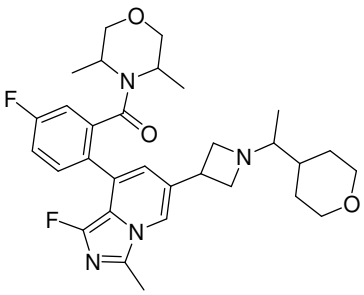

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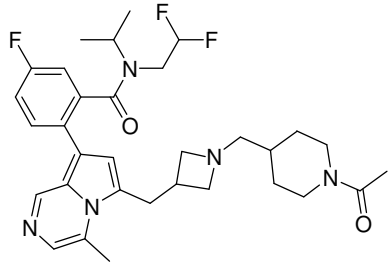

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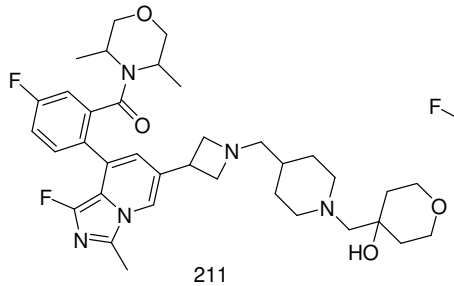

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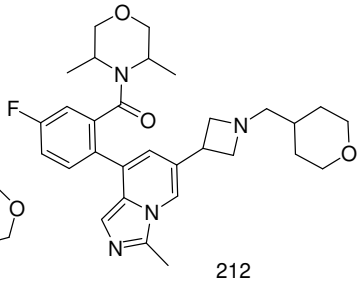

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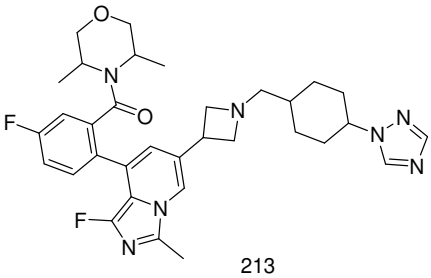

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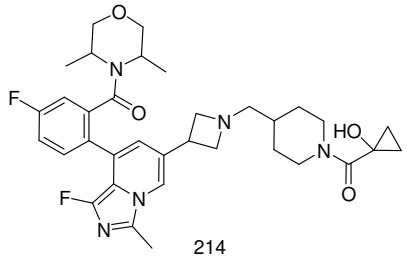

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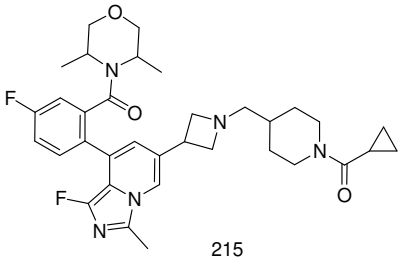

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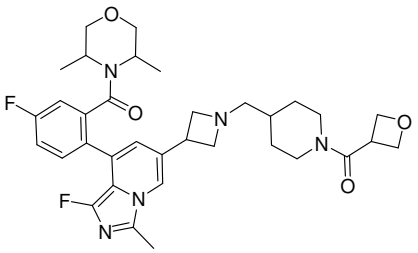

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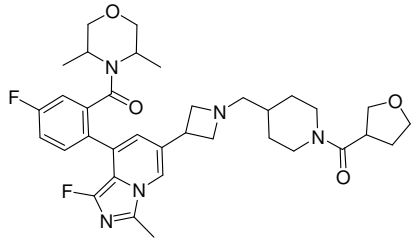

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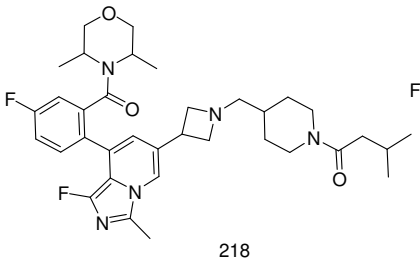

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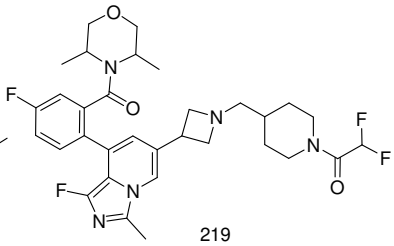

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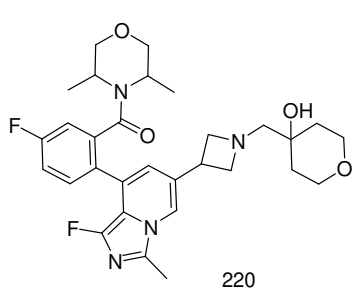

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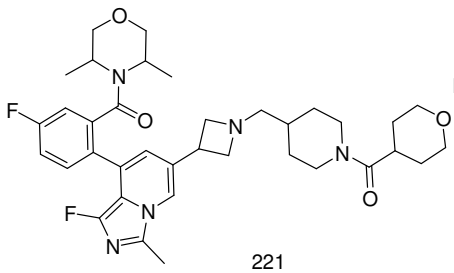

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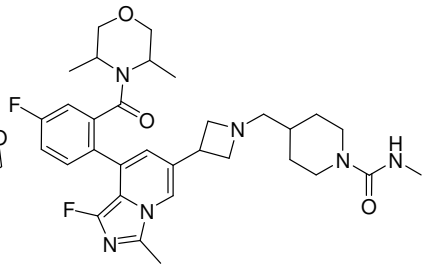

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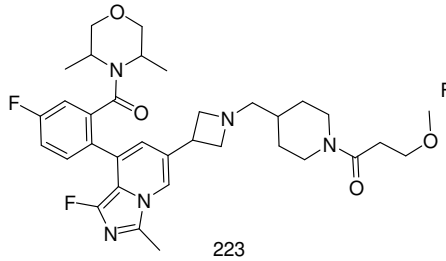

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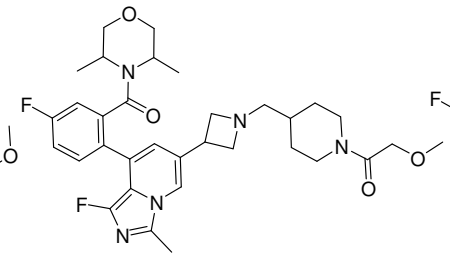

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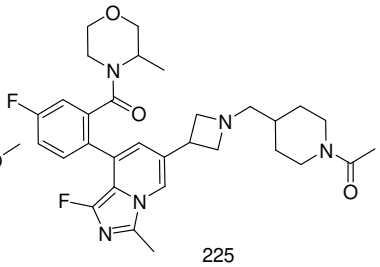

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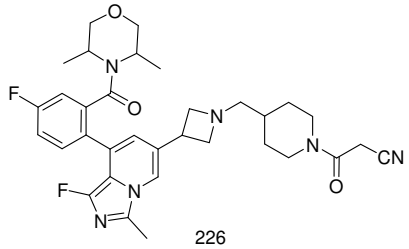

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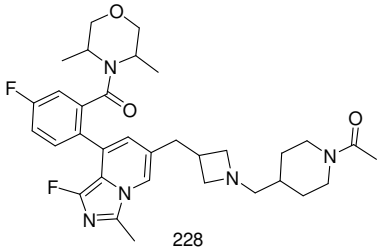

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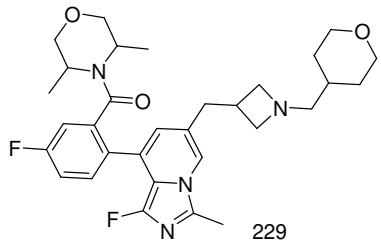

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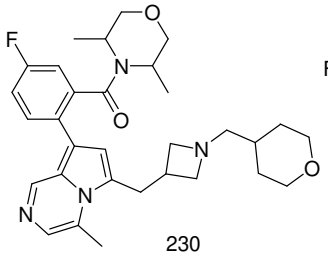

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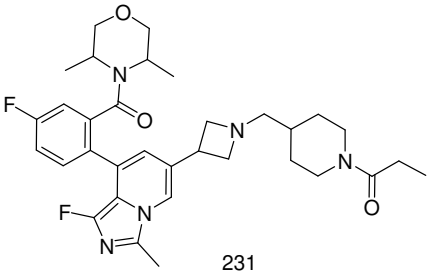

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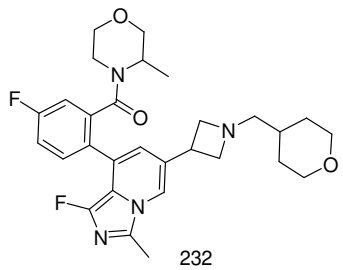

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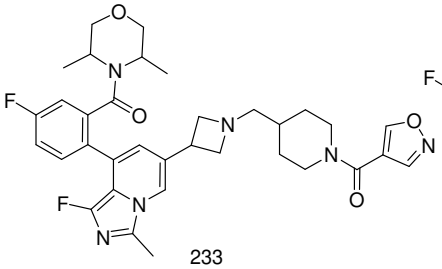

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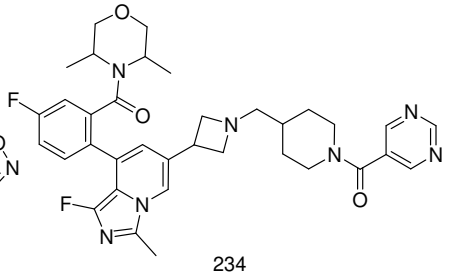

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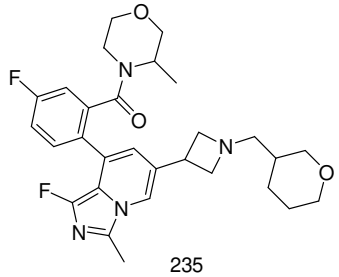

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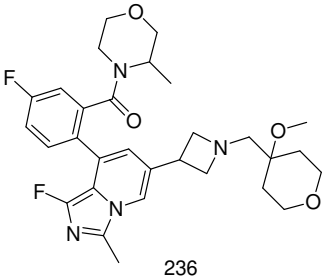

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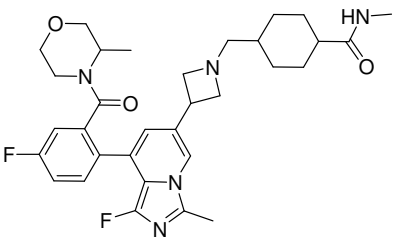

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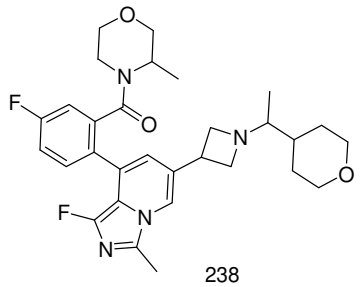

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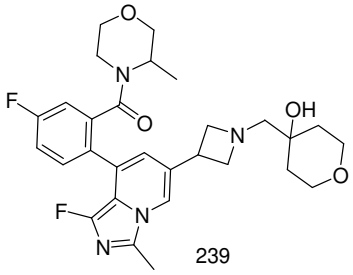

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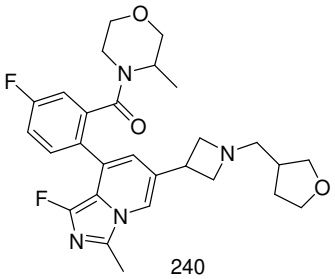

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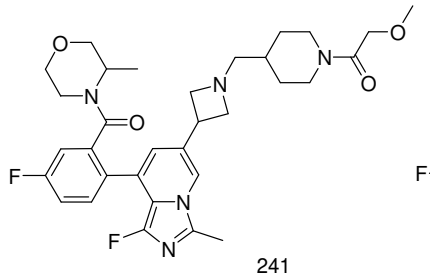

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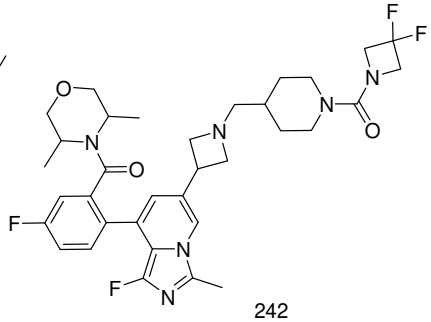

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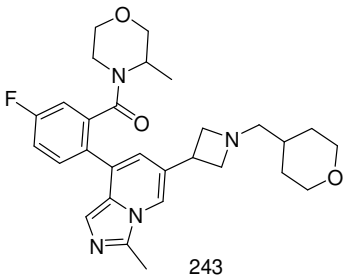

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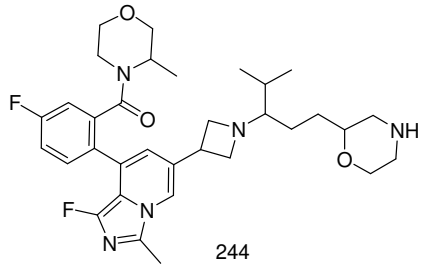

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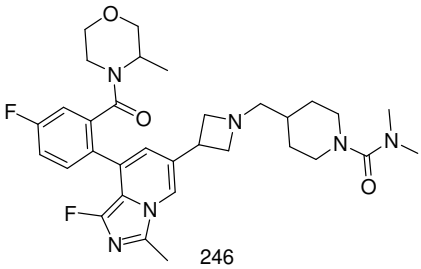

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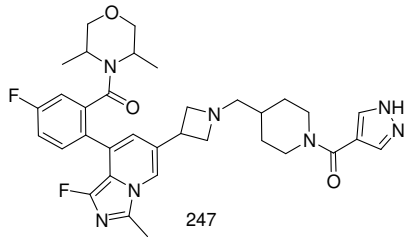

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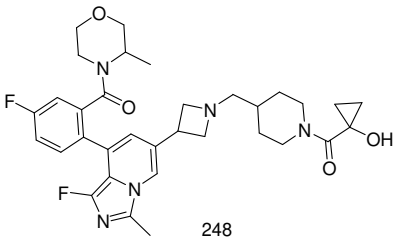

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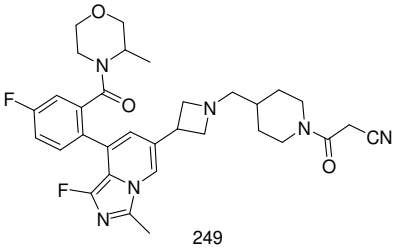

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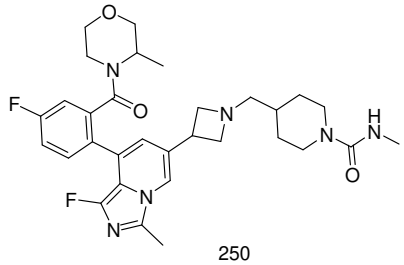

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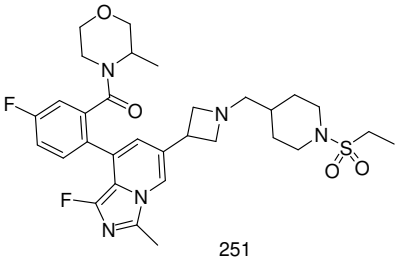

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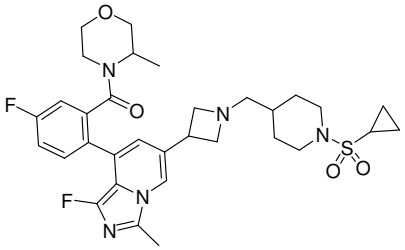

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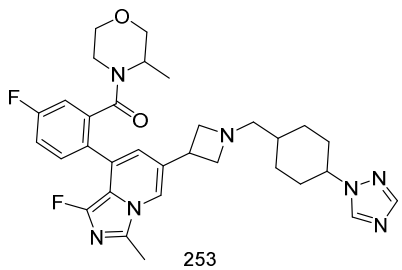

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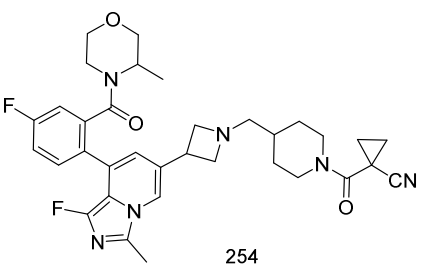

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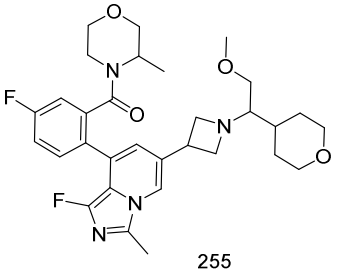

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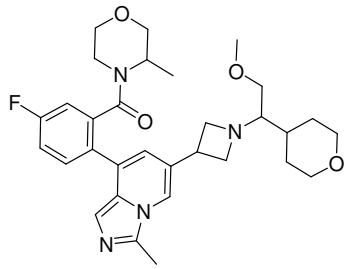

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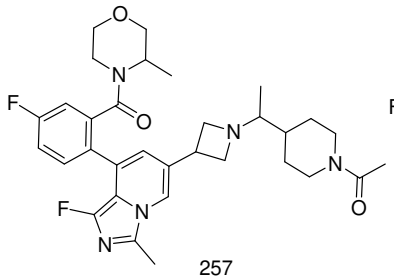

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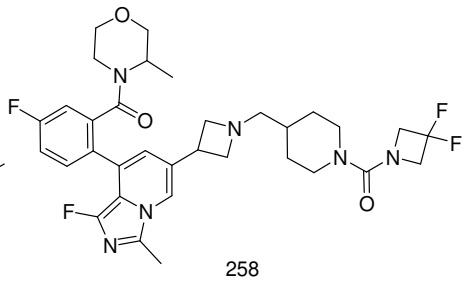

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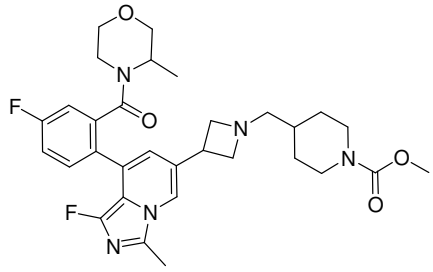

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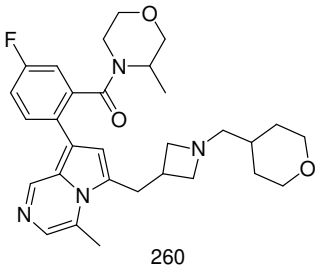

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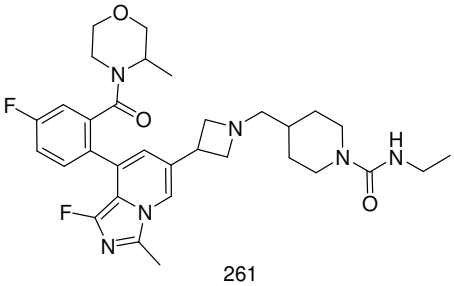

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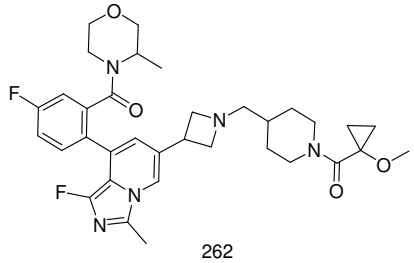

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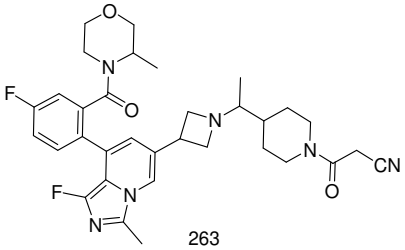

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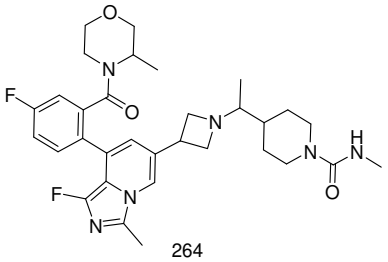

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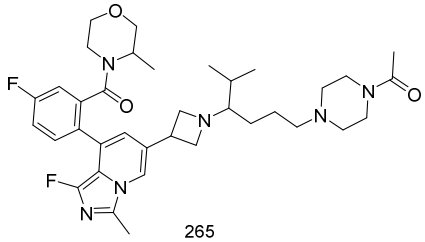

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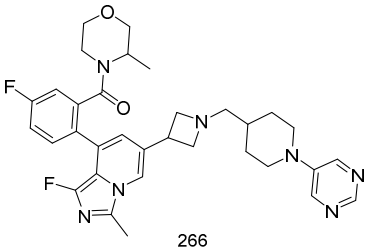

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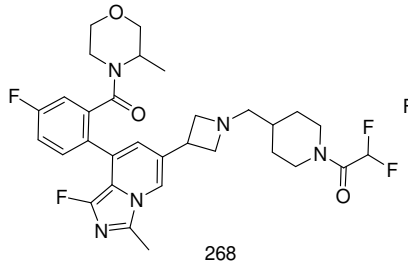

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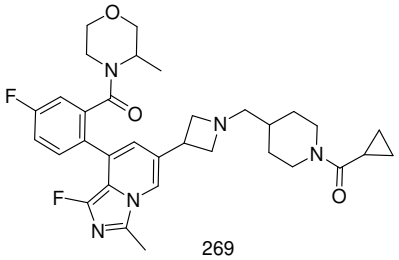

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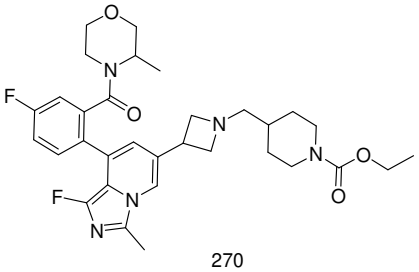

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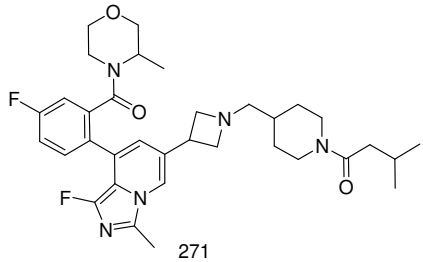

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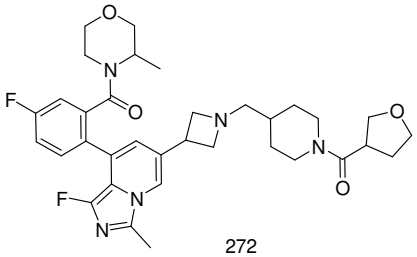

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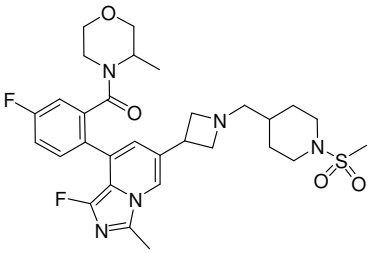

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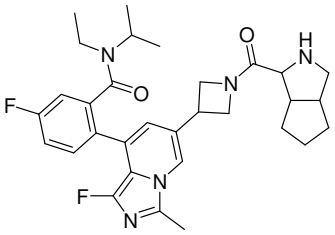

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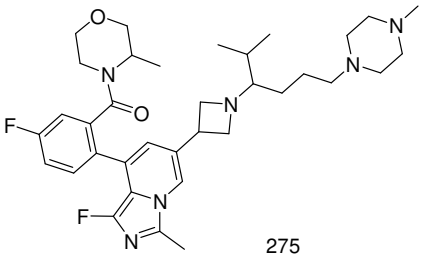

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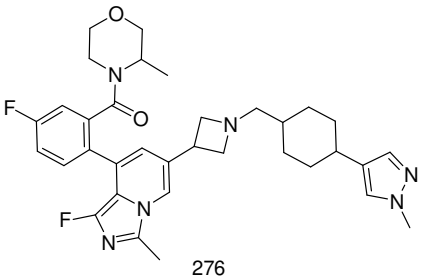

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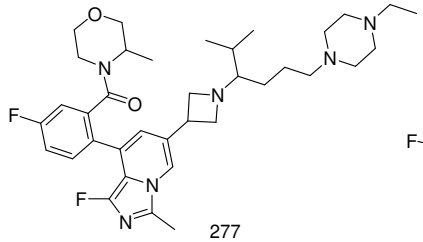

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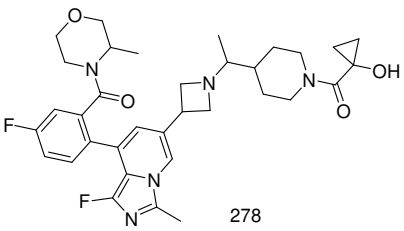

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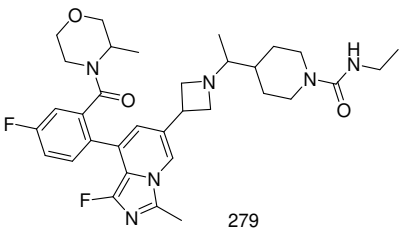

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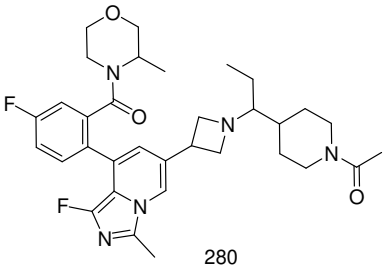

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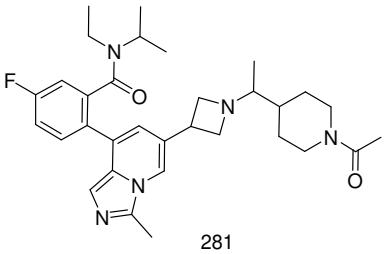

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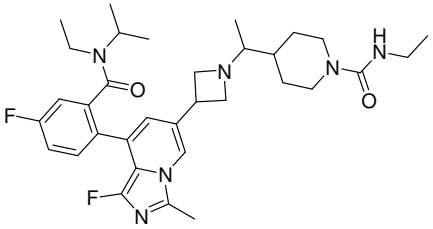

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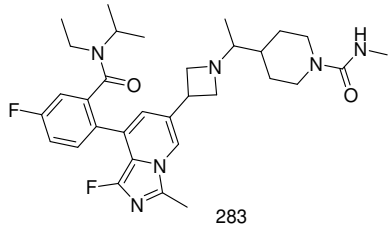

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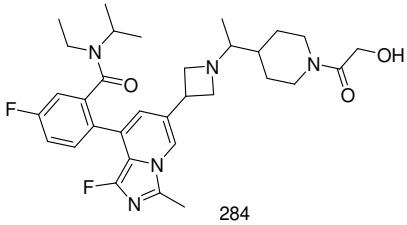

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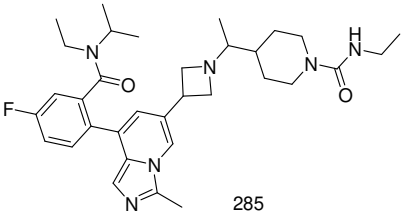

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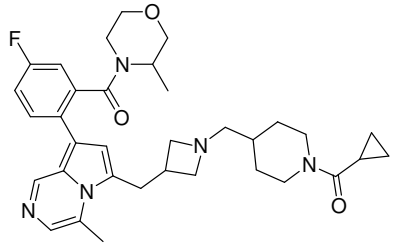

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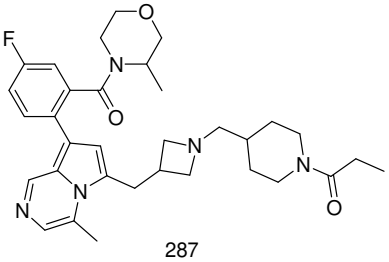

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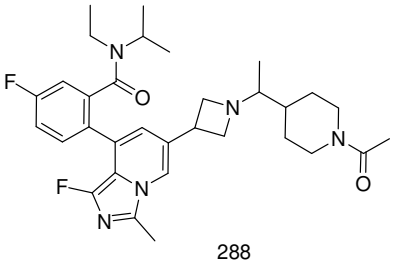

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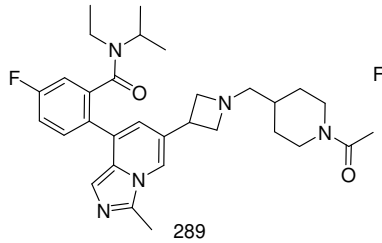

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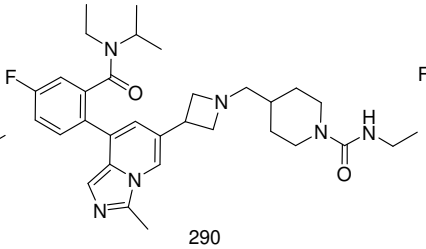

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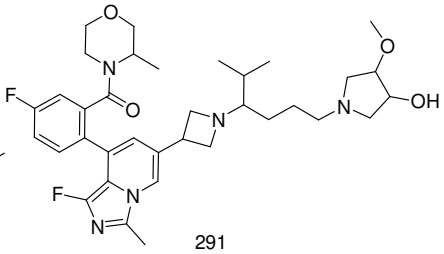

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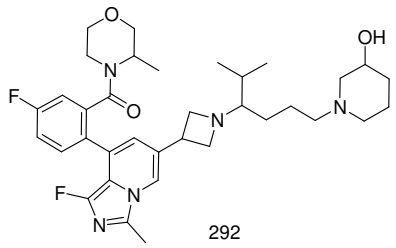

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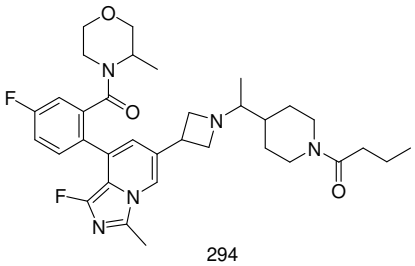

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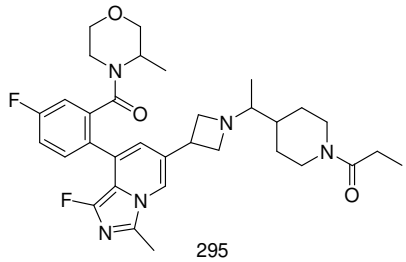

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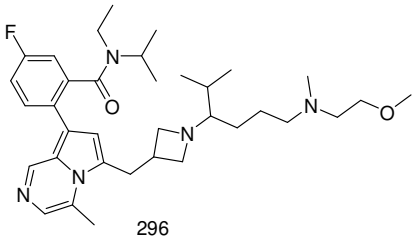

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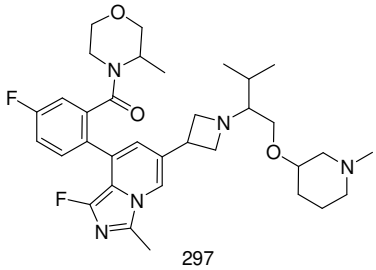

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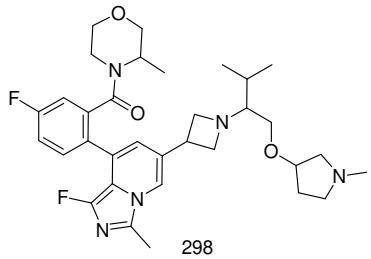

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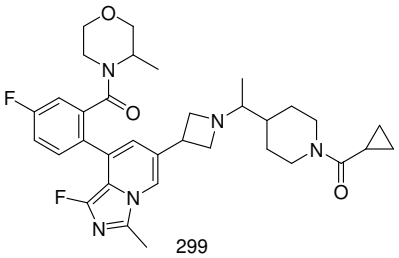

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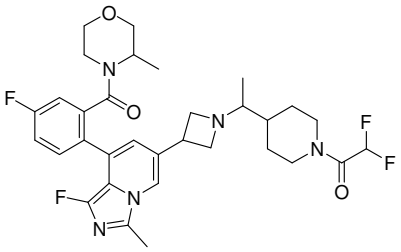

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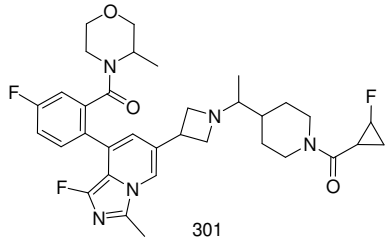

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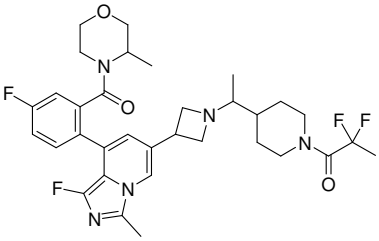

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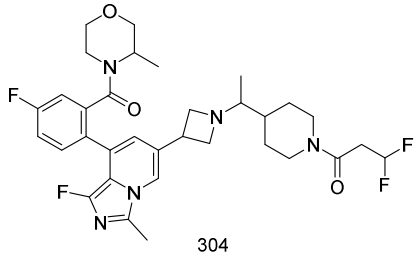

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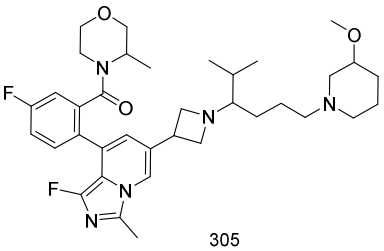

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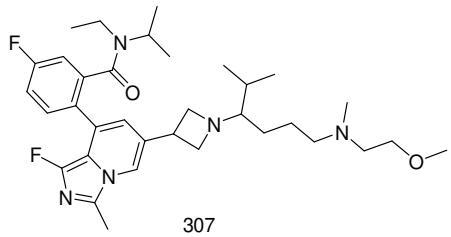

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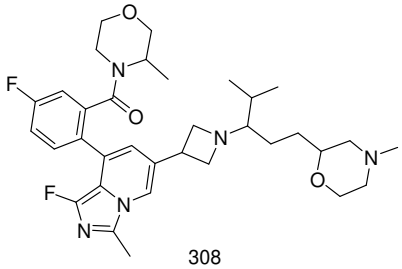

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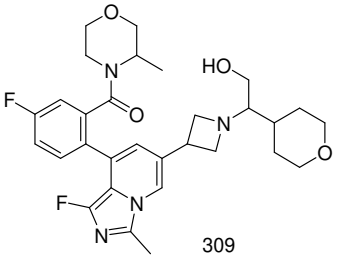

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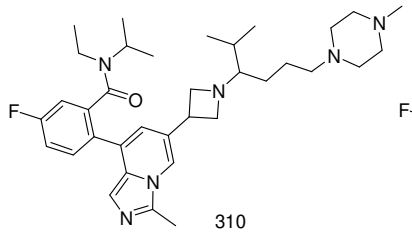

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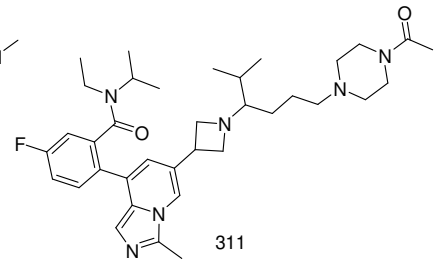

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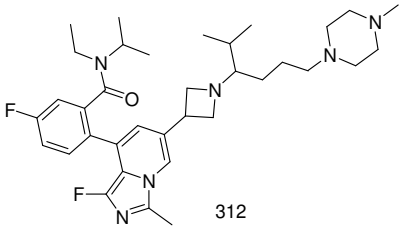

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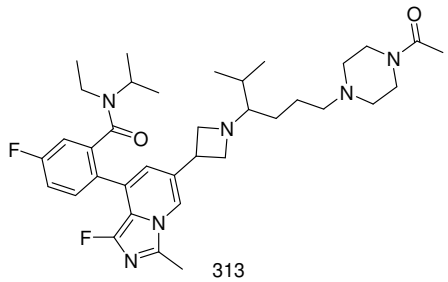

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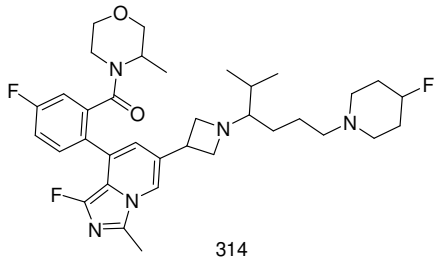

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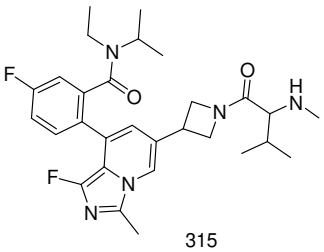

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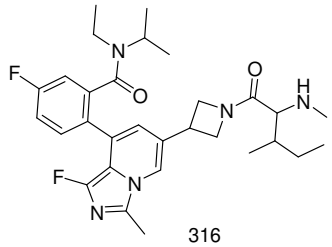

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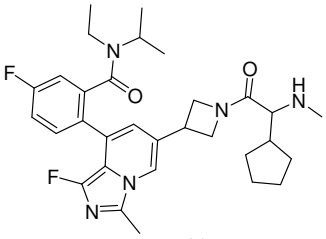

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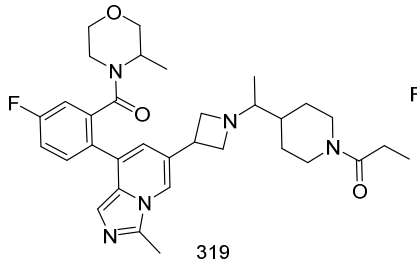

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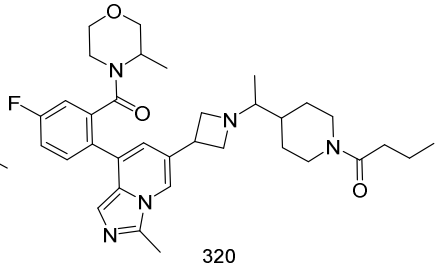

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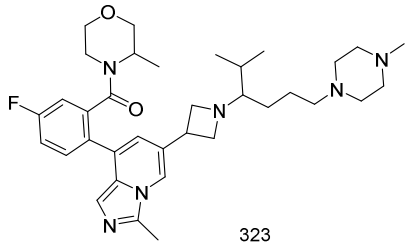

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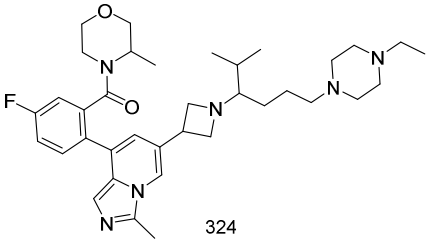

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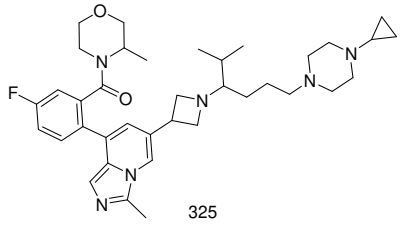

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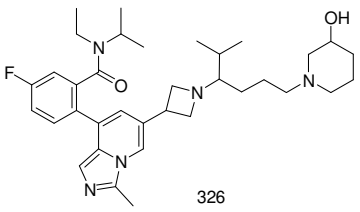

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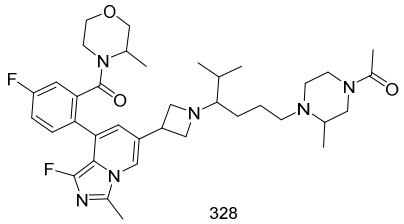

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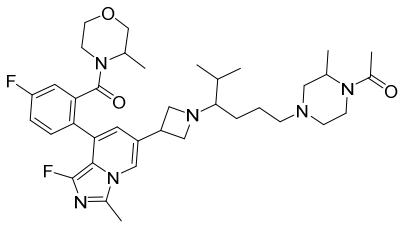

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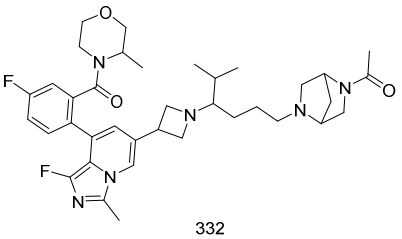

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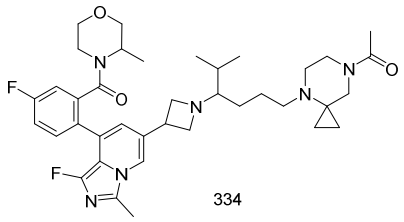

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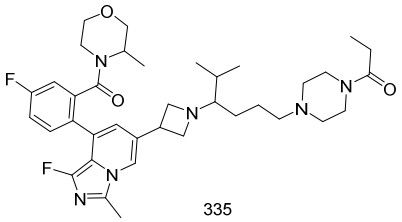

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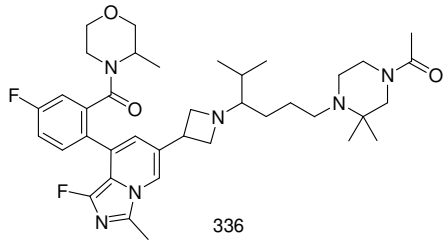

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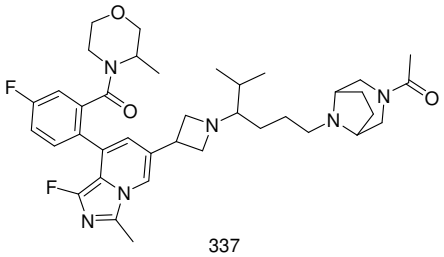

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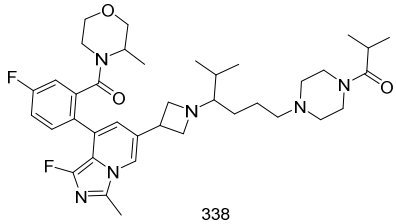

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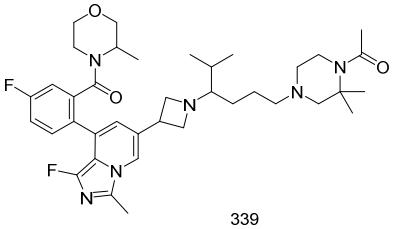

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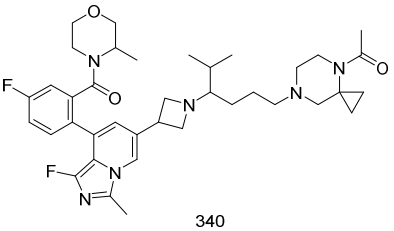

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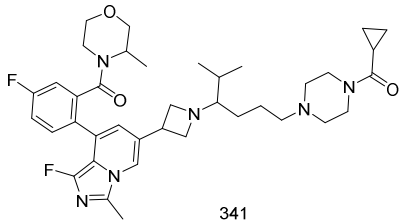

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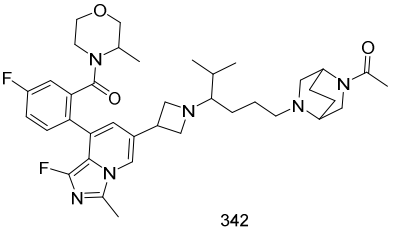

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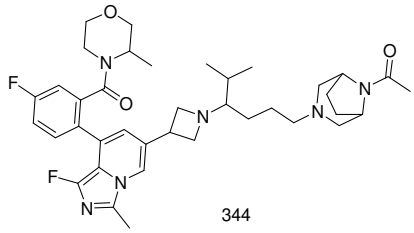

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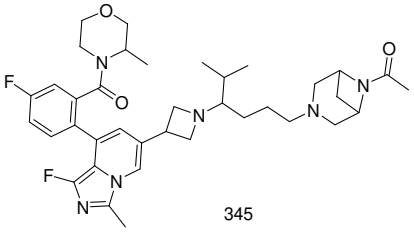

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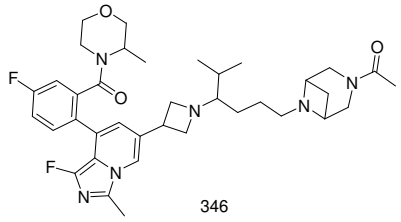

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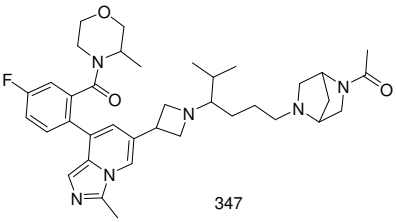

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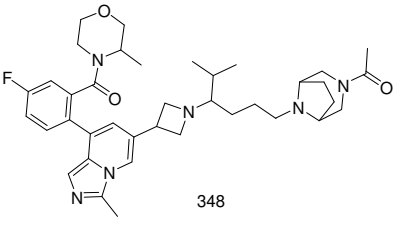

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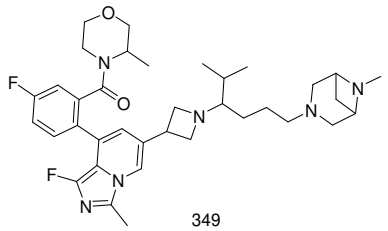

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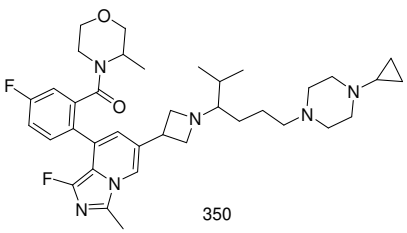

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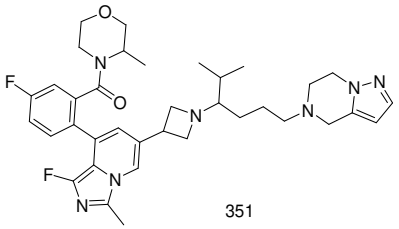

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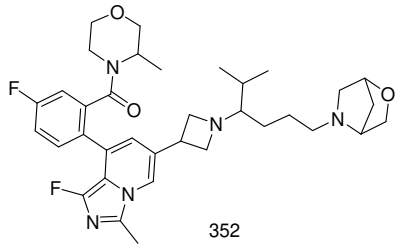

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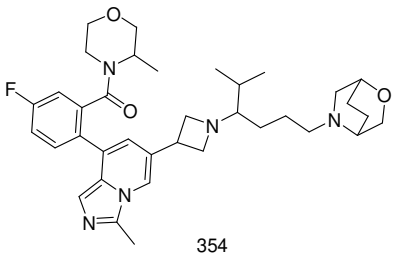

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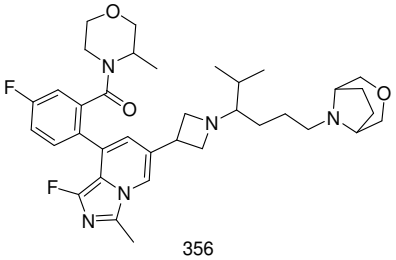

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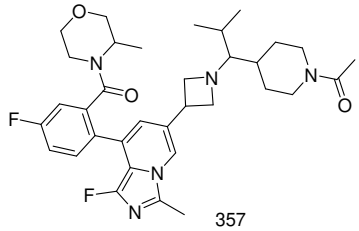

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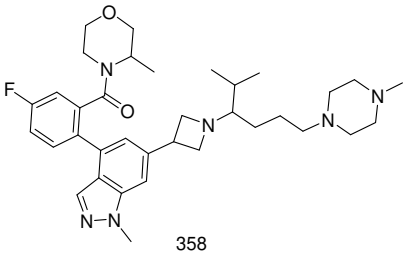

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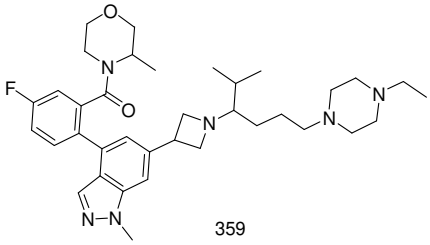

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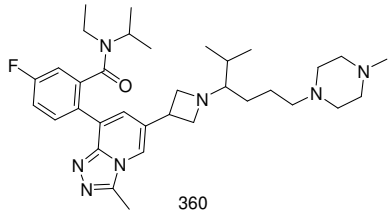

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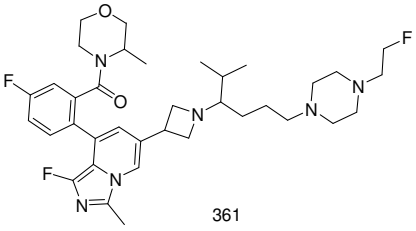

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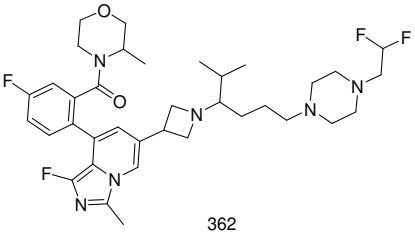

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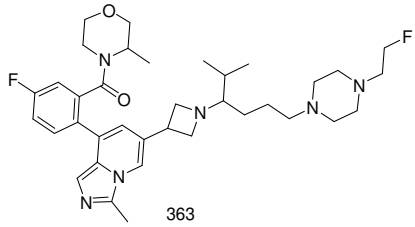

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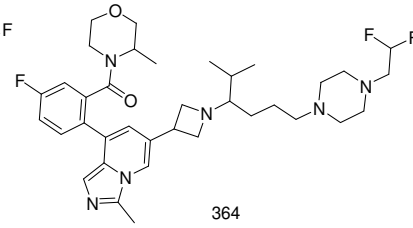

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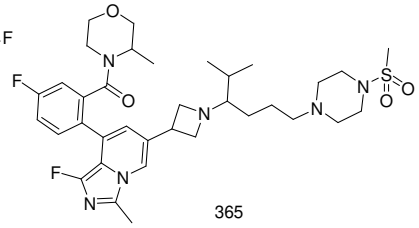

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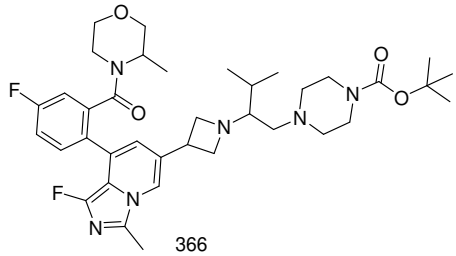

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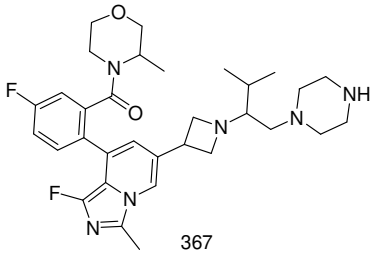

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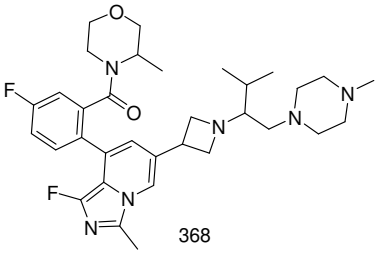

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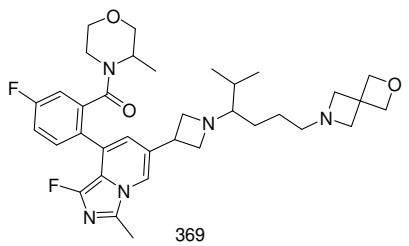

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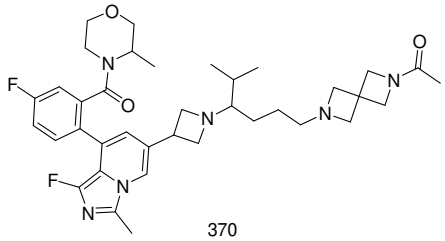

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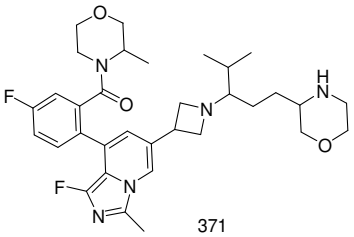

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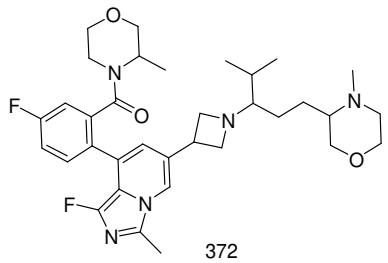

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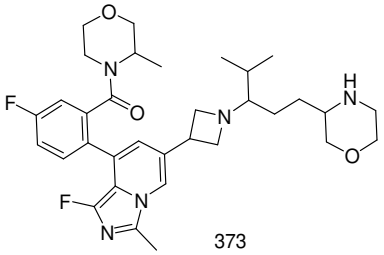

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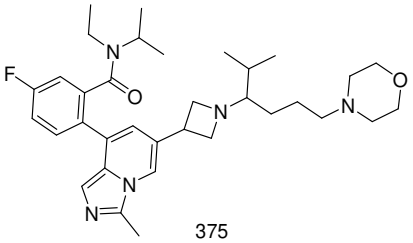

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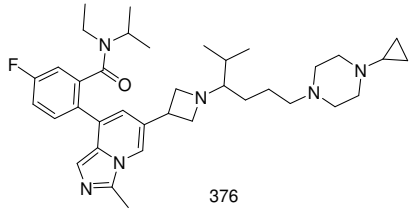

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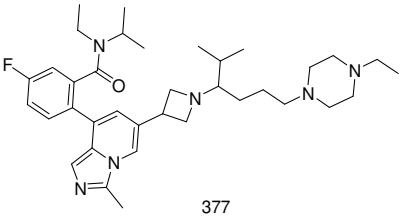

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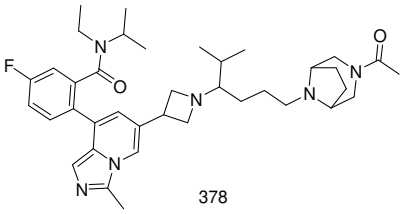

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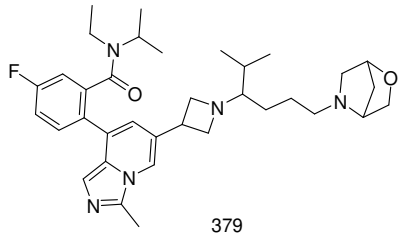

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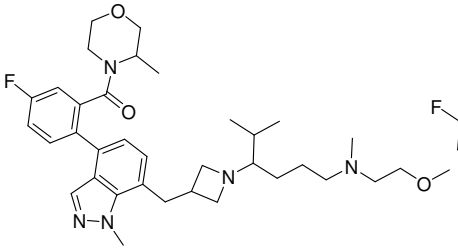

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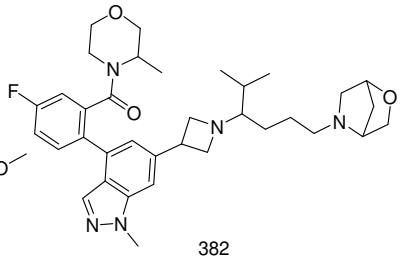

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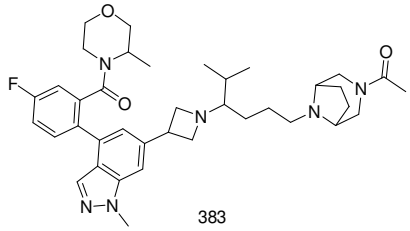

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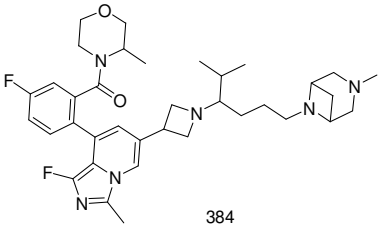

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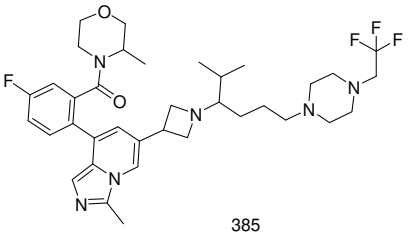

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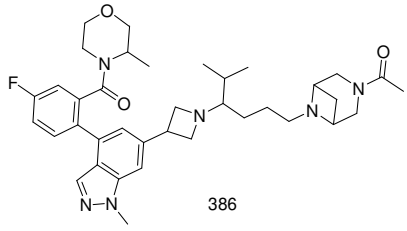

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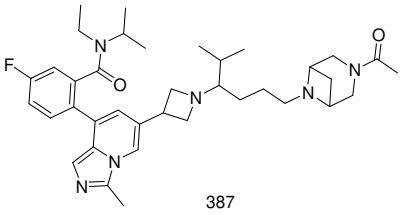

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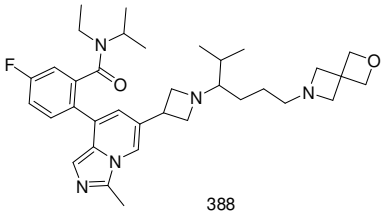

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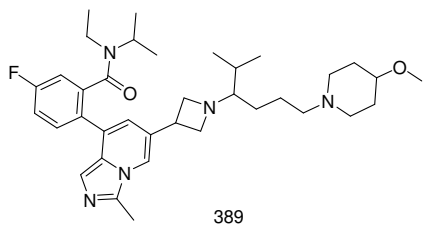

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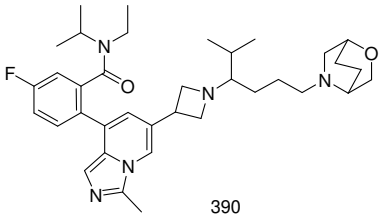

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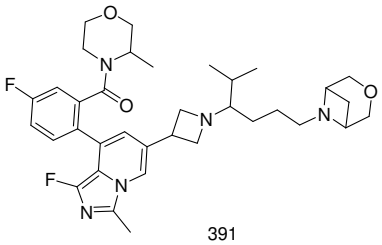

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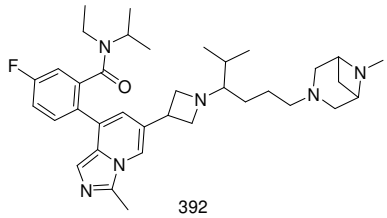

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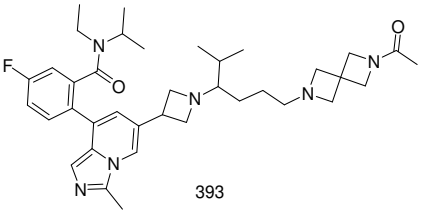

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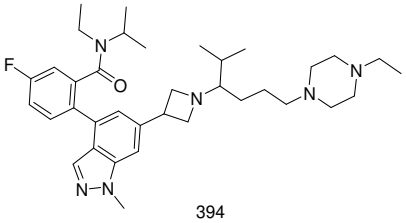

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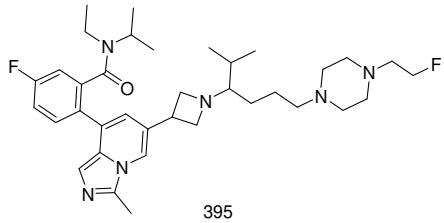

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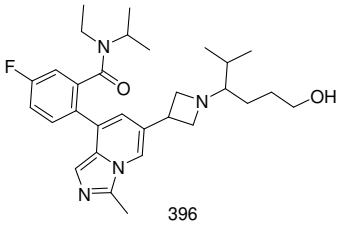

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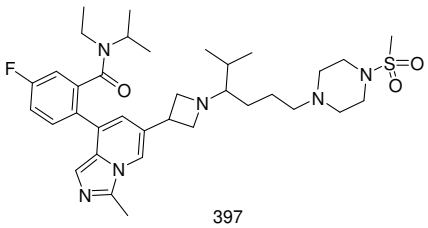

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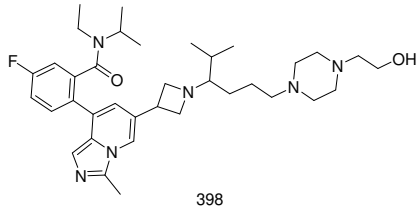

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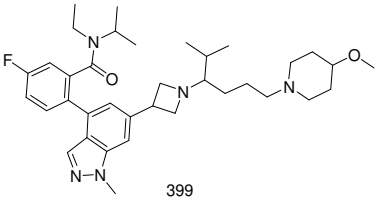

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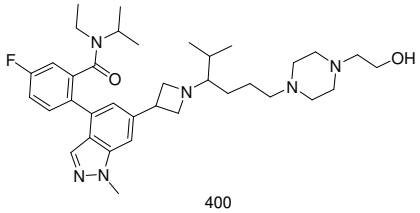

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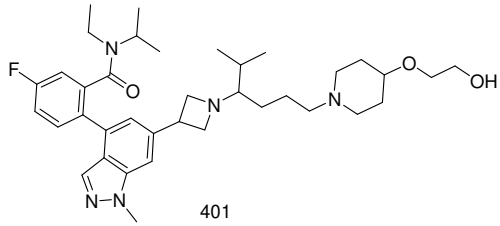

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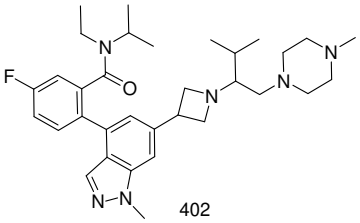

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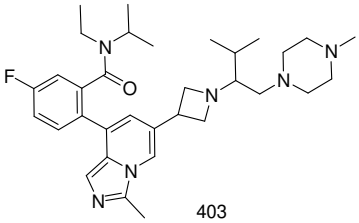

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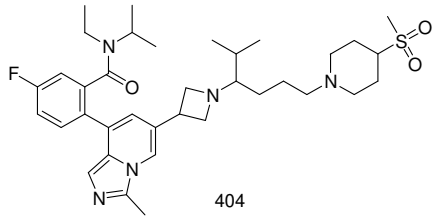

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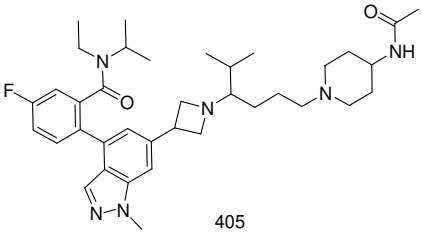

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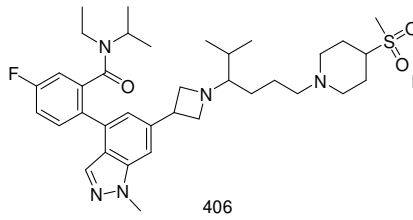

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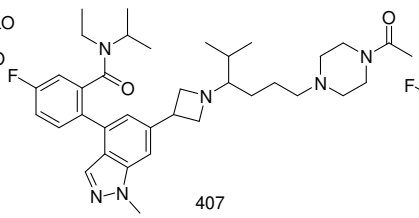

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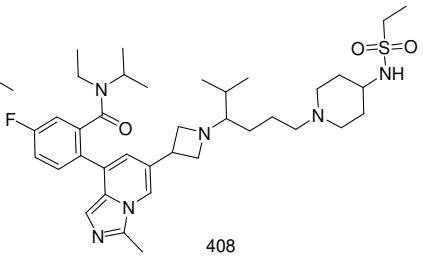

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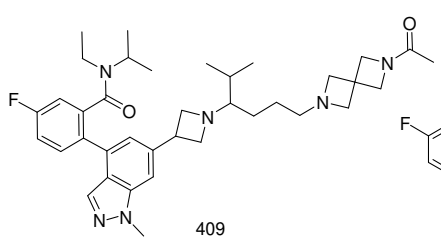

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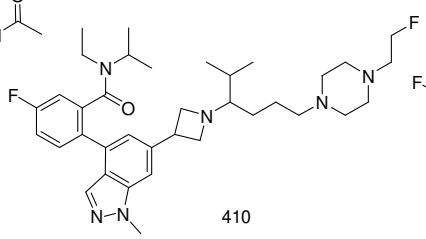

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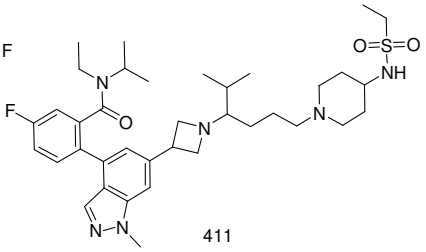

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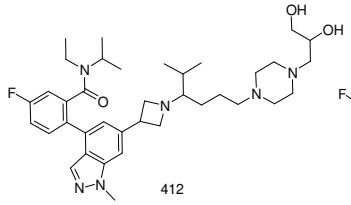

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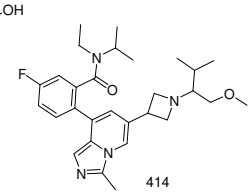

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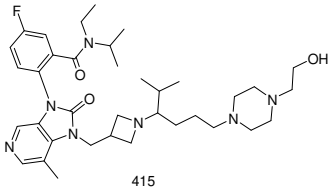

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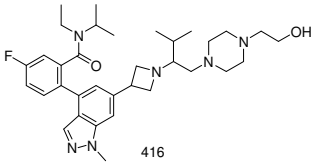

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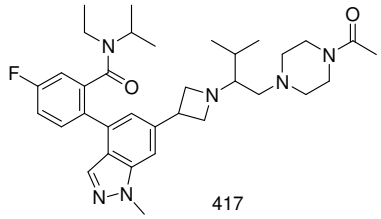

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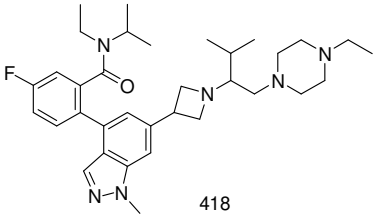

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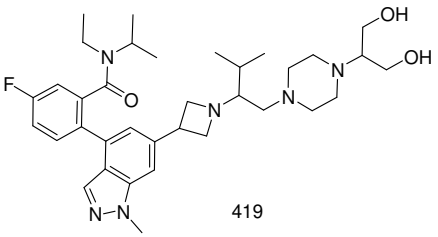

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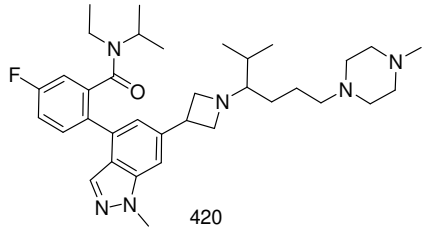

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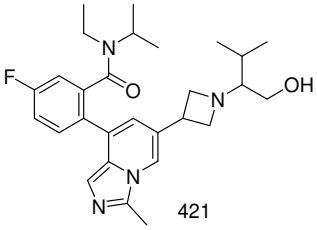

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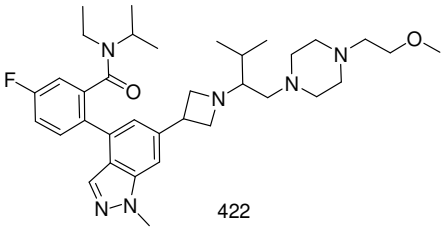

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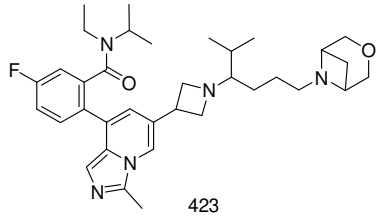

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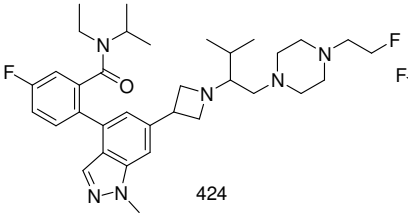

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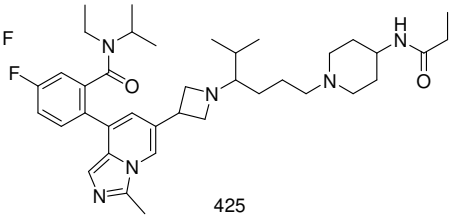

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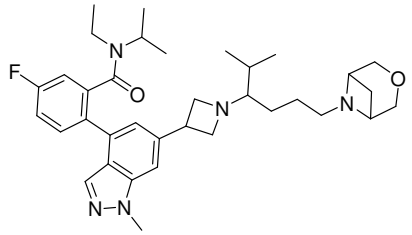

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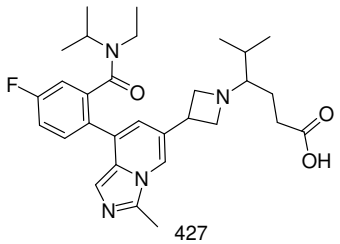

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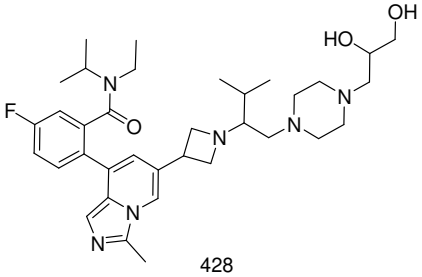

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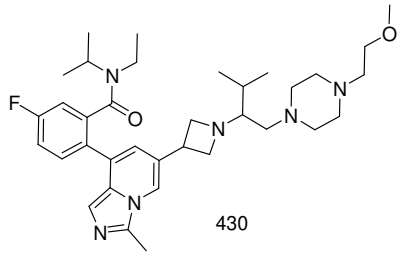

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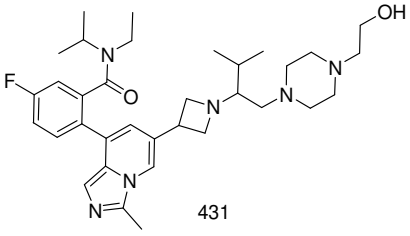

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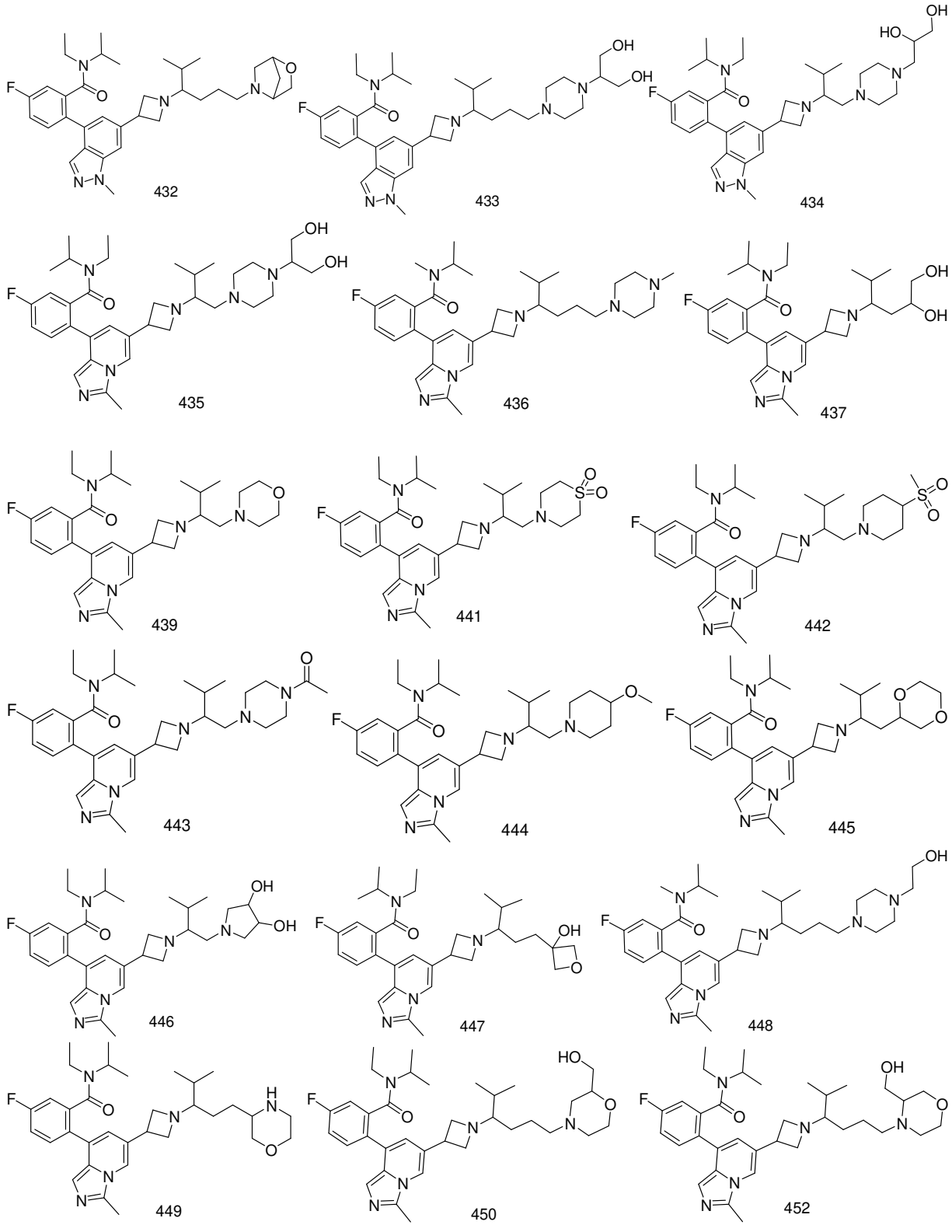
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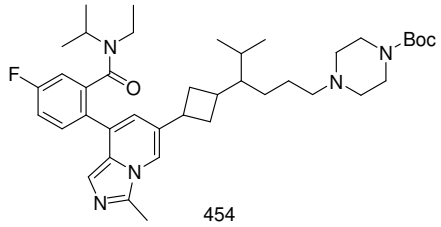

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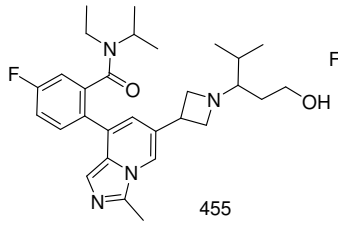

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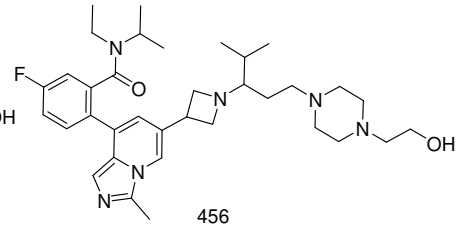

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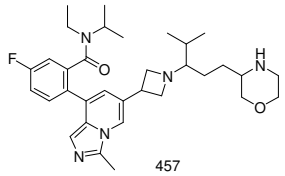

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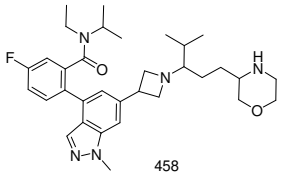

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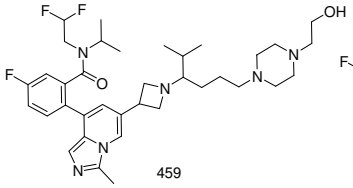

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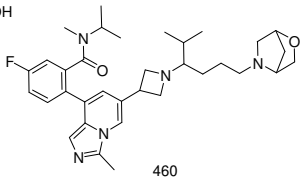

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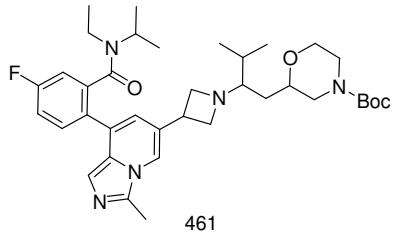

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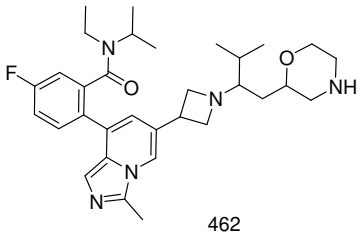

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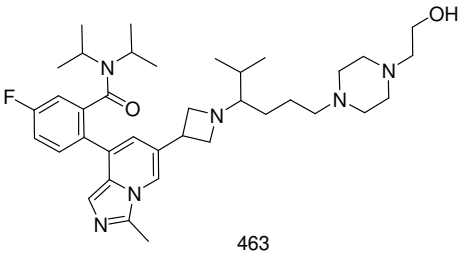

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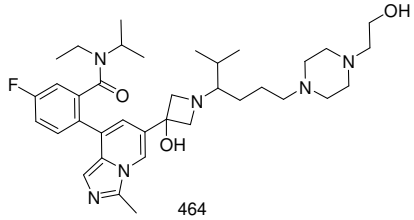

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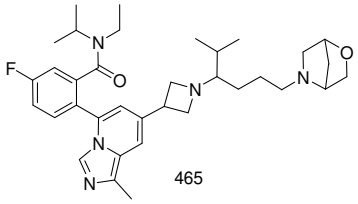

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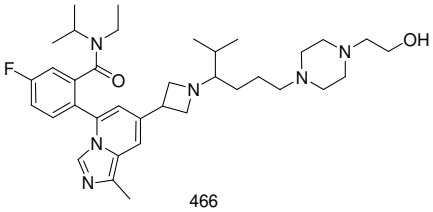

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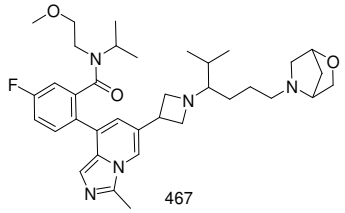

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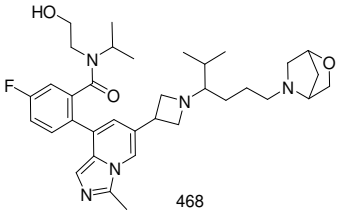

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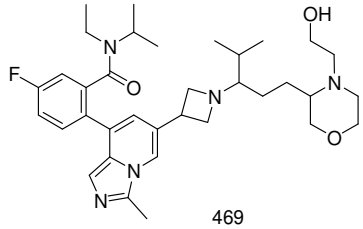

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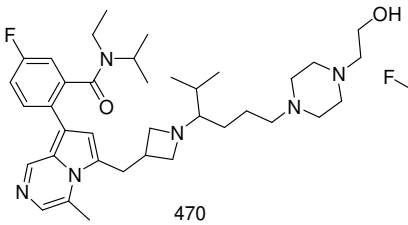

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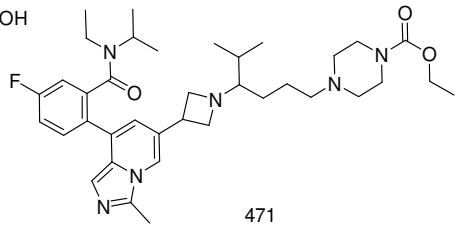

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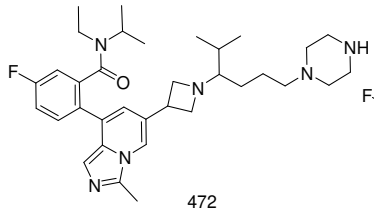

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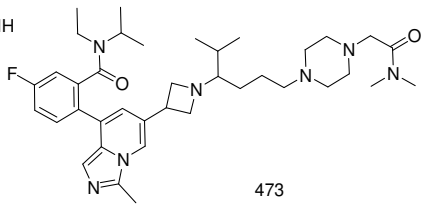

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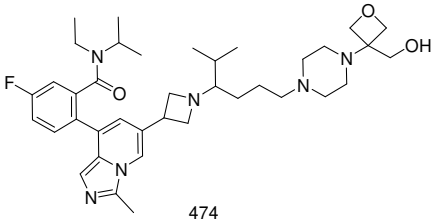

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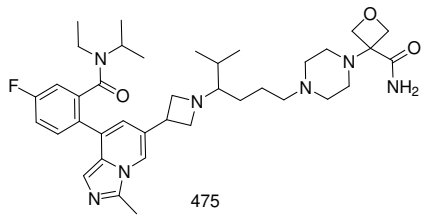

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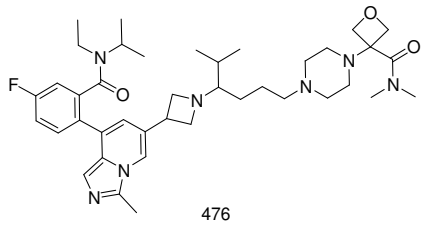

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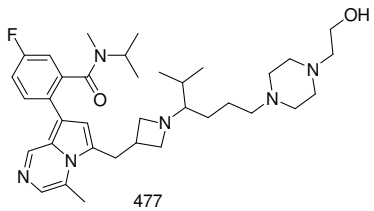

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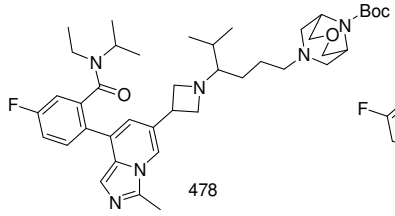

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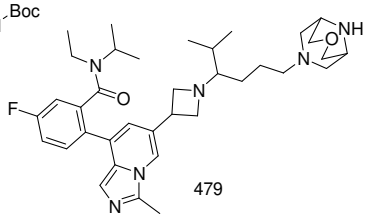

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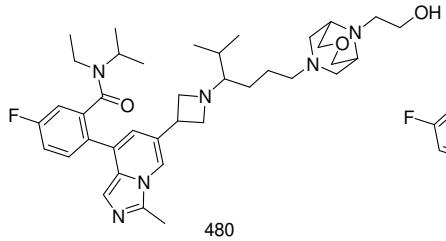

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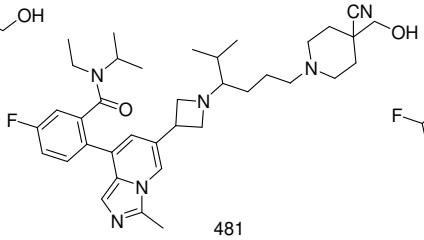

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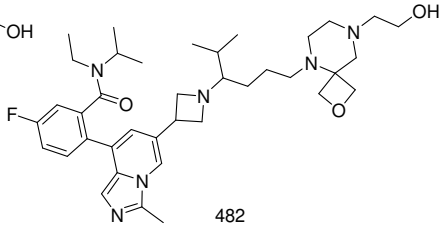

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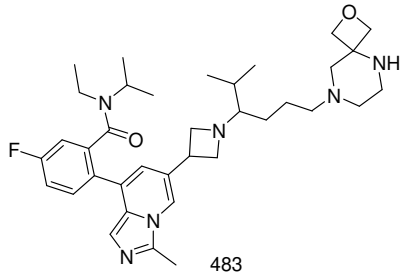

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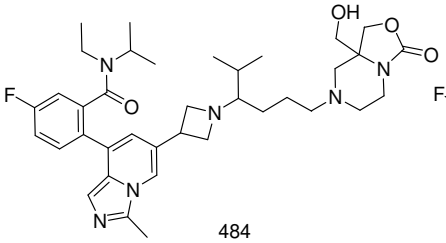

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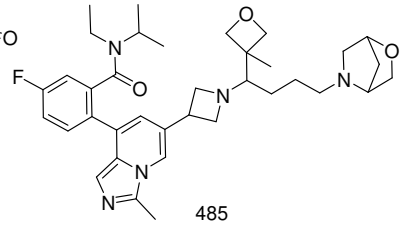

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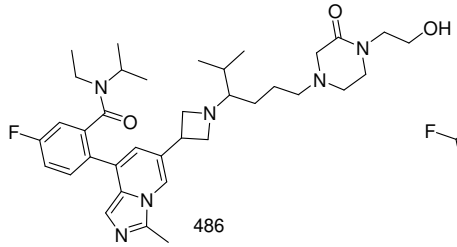

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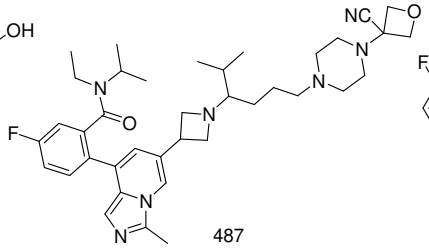

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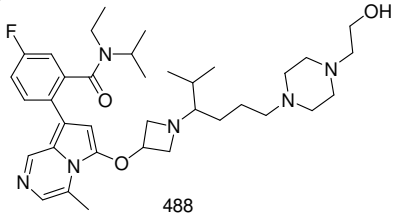

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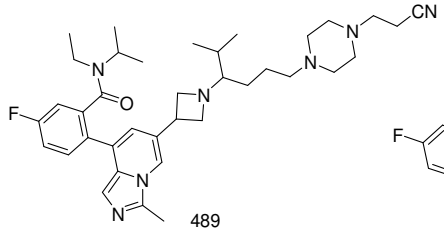

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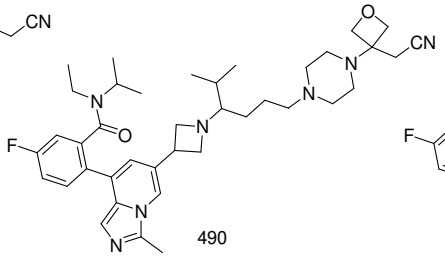

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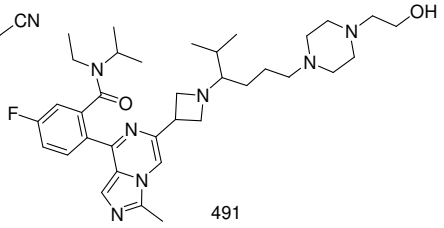

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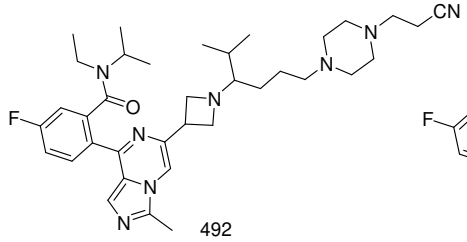

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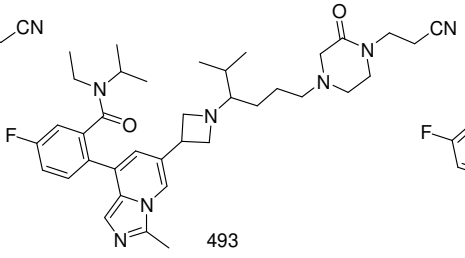

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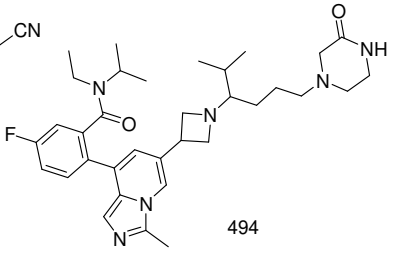

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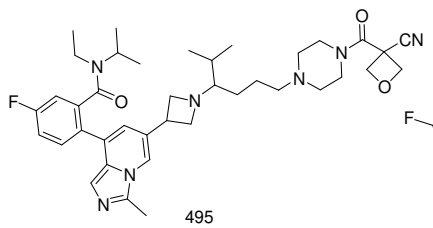

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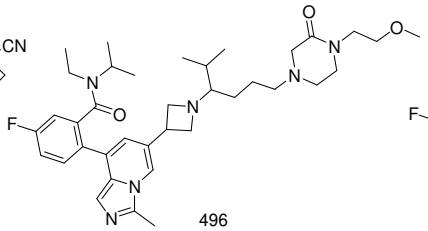

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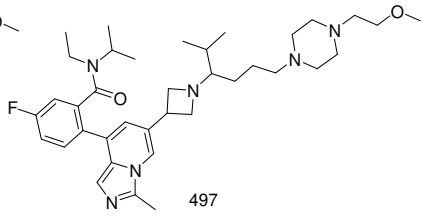

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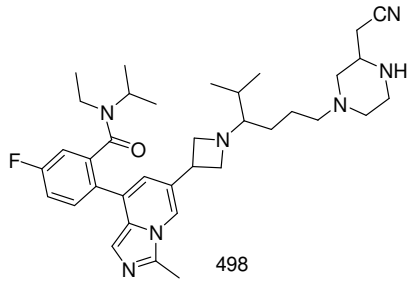

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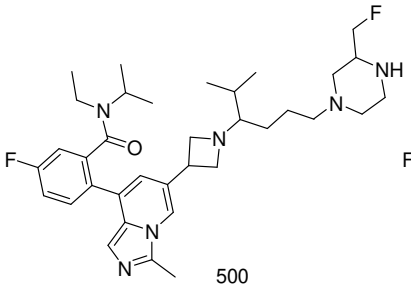

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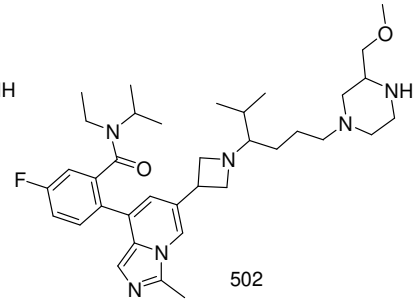

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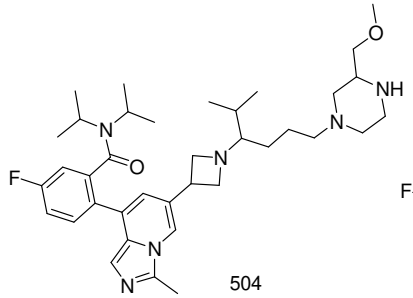

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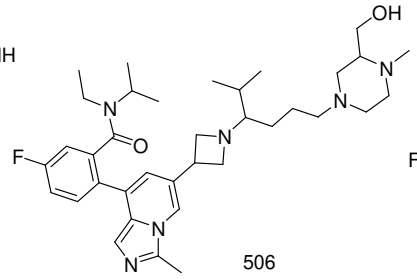

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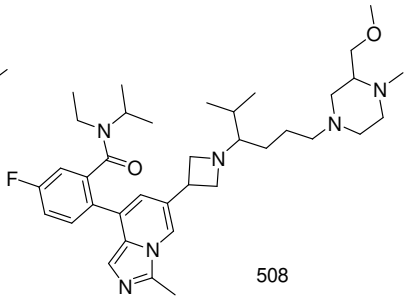

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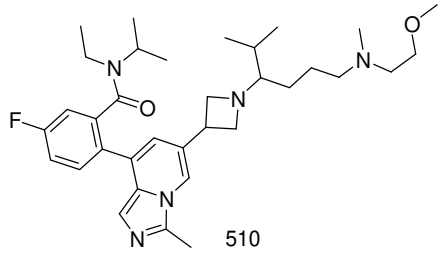

510

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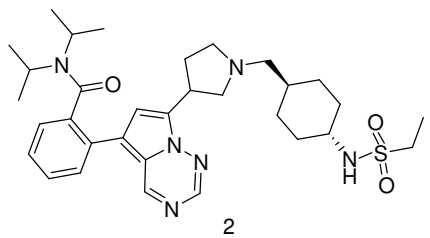
In some embodiments of the present invention, the stereoisomer has a structure of:



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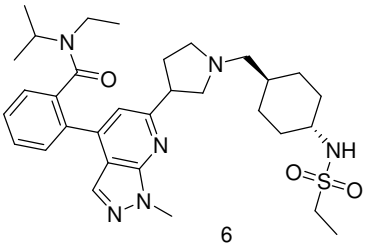

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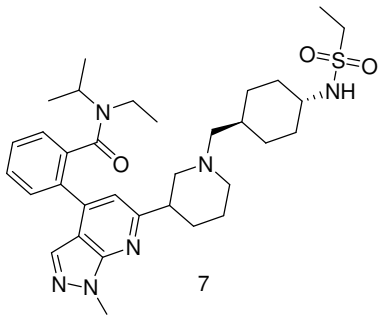

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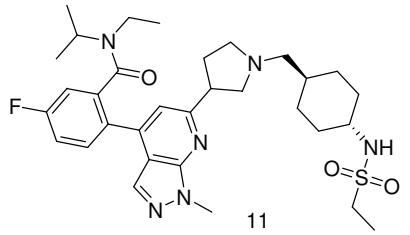

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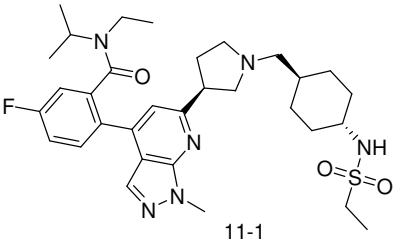

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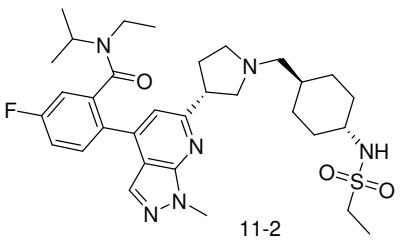

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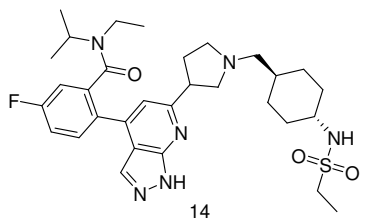

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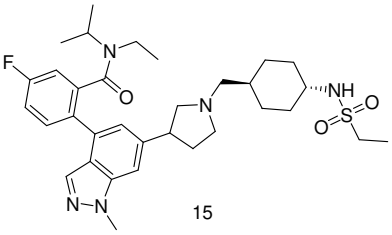

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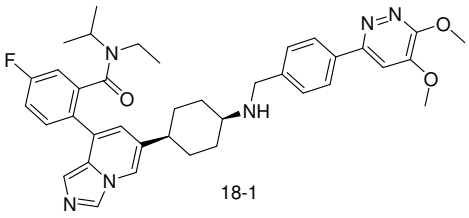

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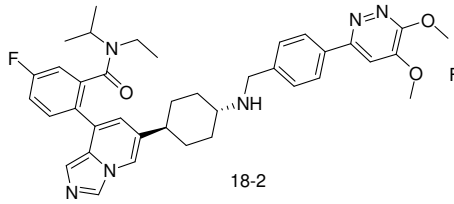

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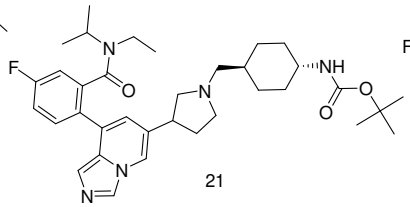

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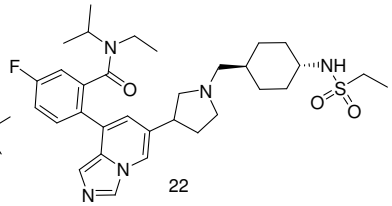

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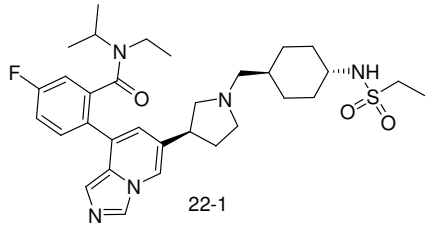

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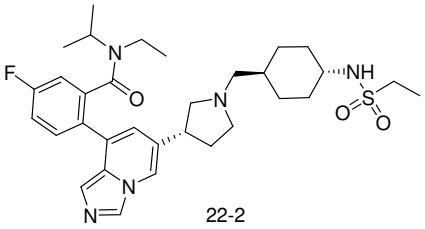

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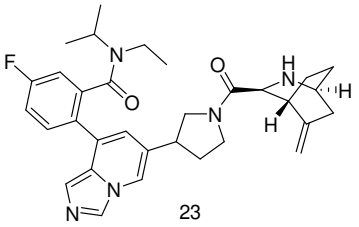

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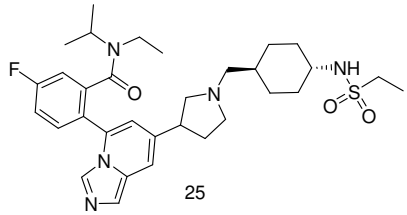

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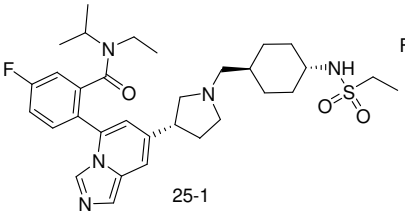

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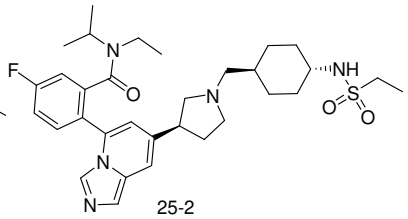

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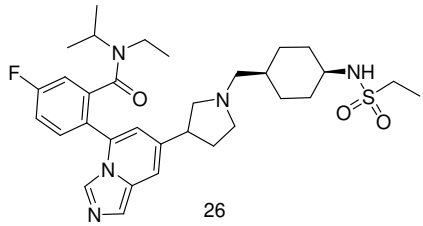

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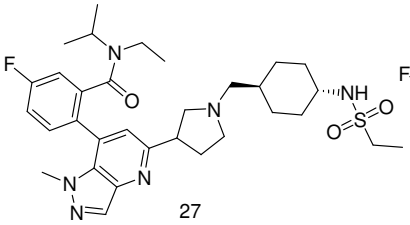

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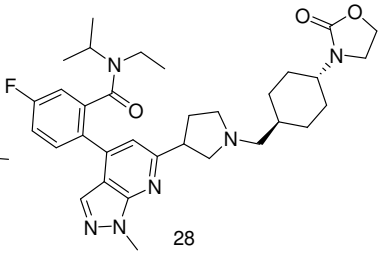

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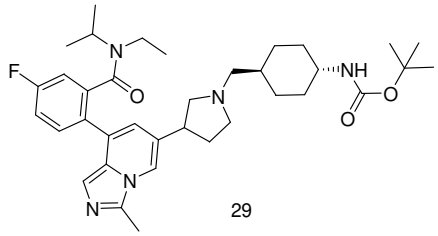

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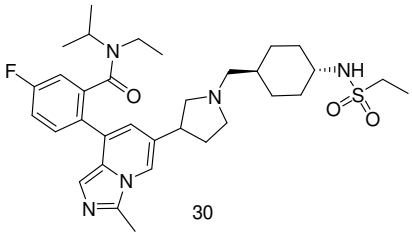

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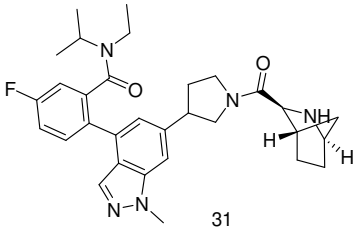

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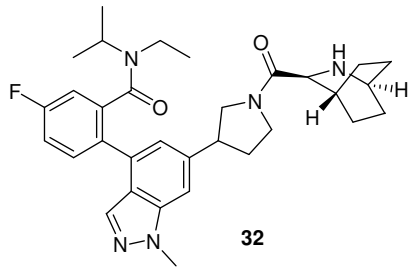

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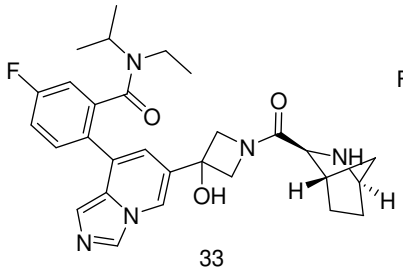

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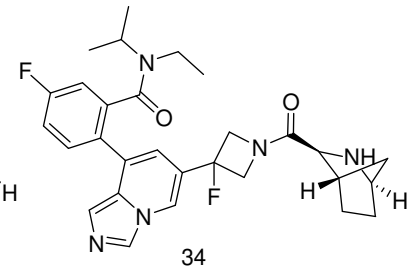

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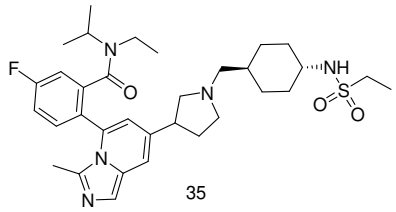

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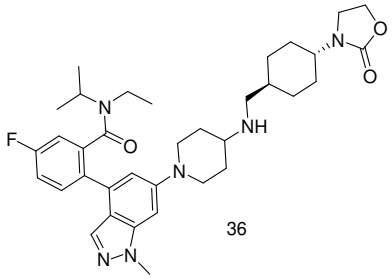

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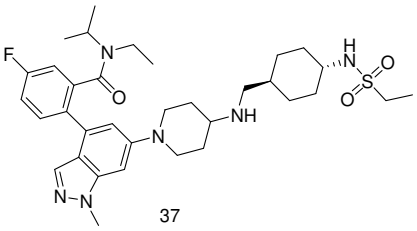

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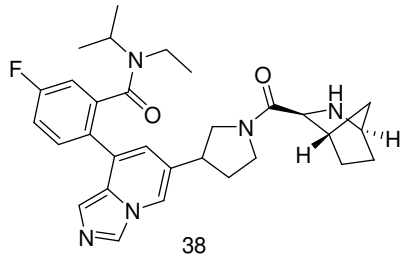

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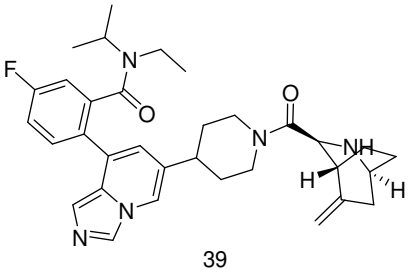

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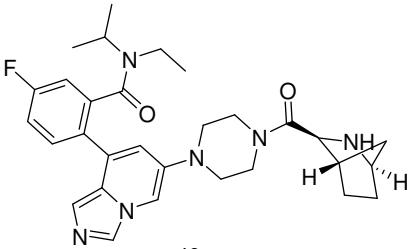

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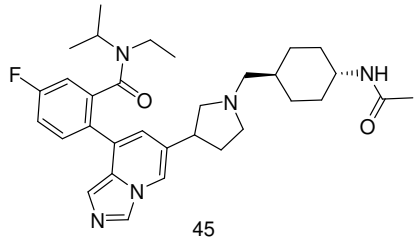

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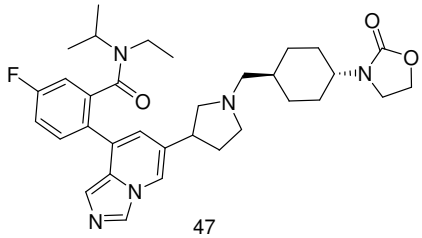

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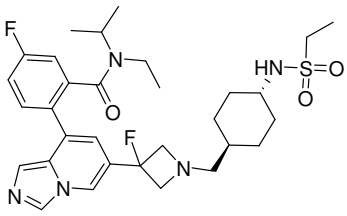

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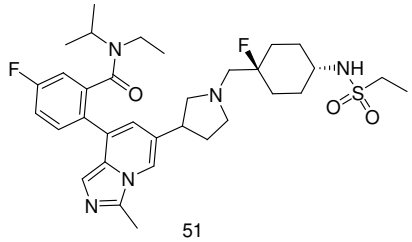

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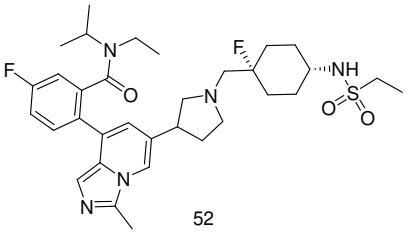

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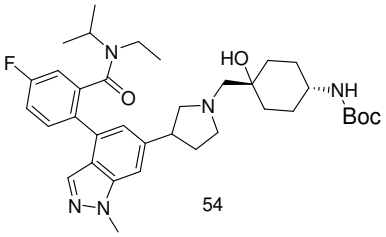

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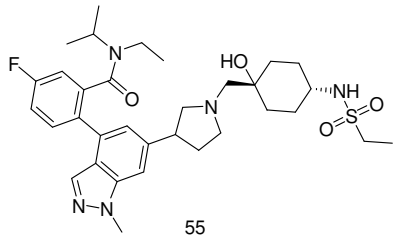

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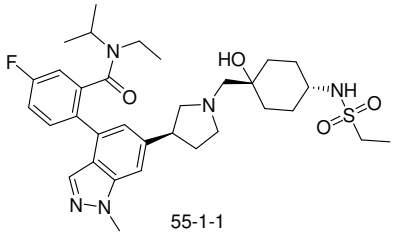

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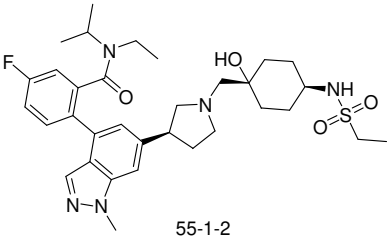

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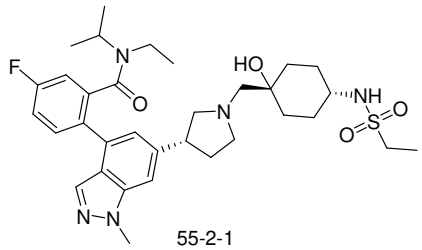

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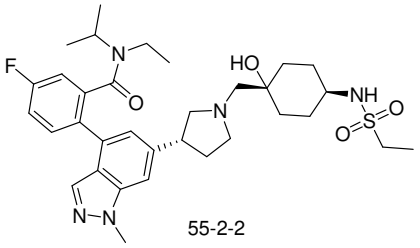

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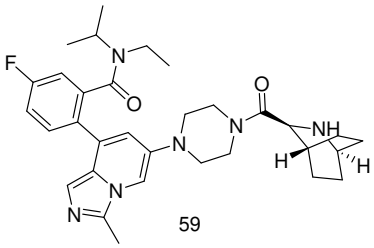

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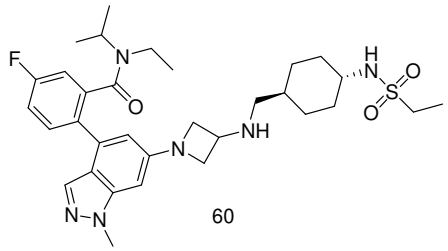

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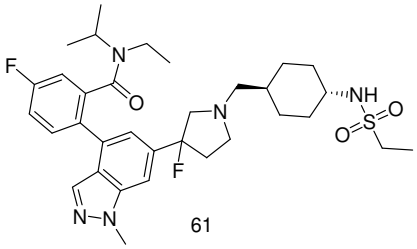

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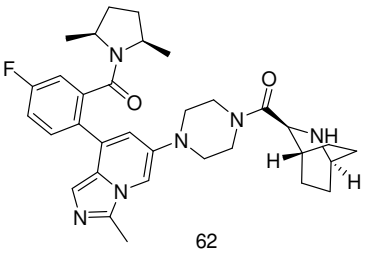

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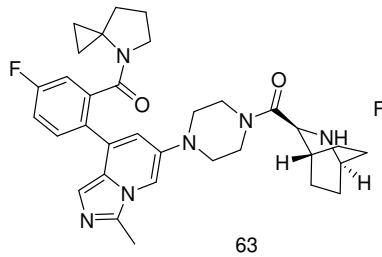

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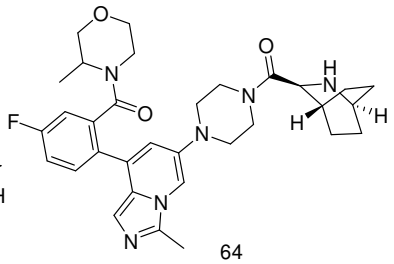

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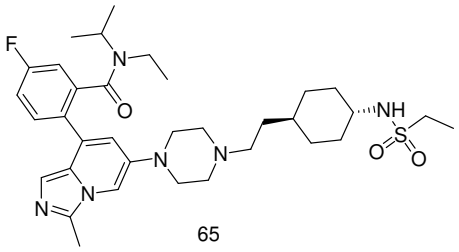

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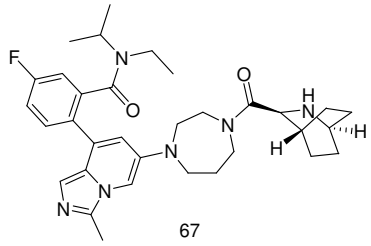

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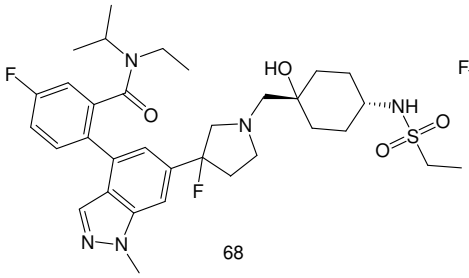

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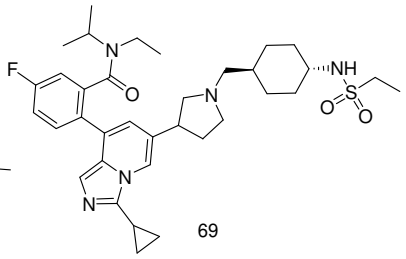

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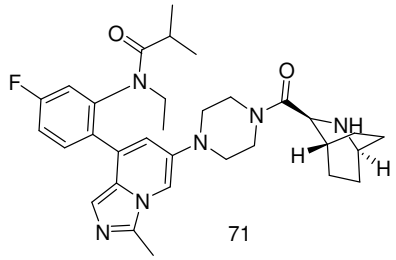

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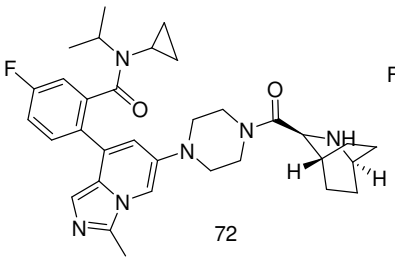

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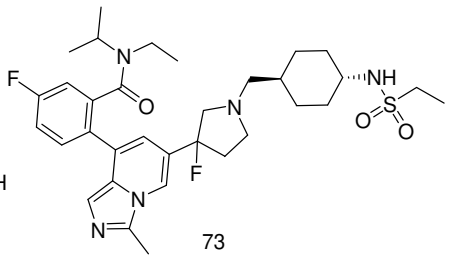

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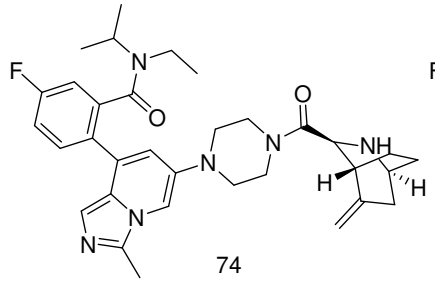

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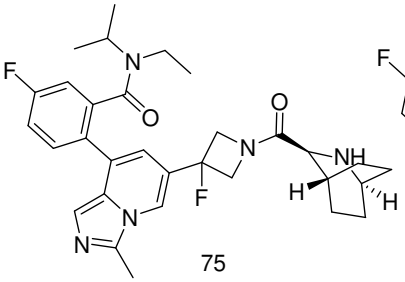

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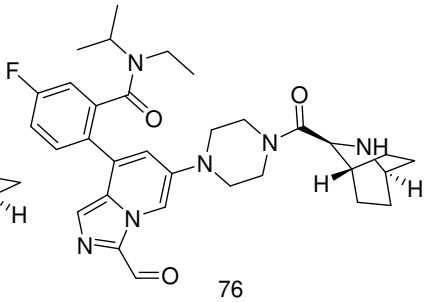

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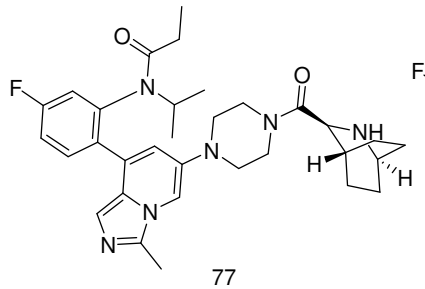

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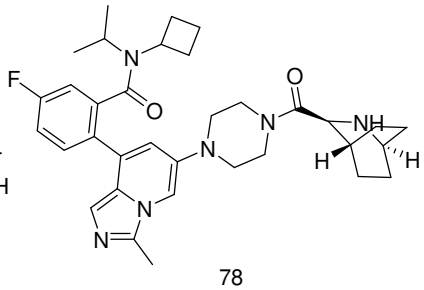

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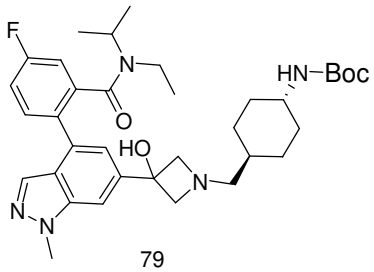

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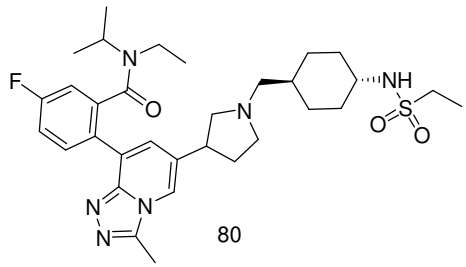

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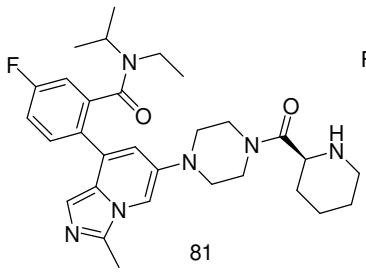

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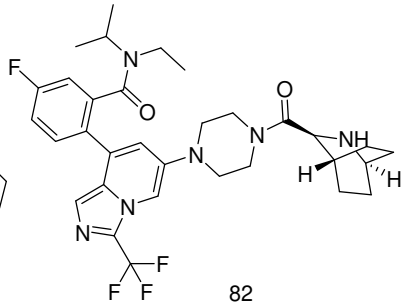

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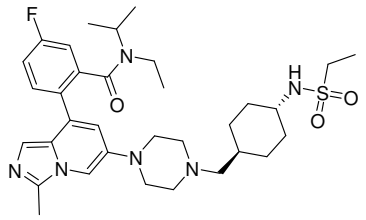

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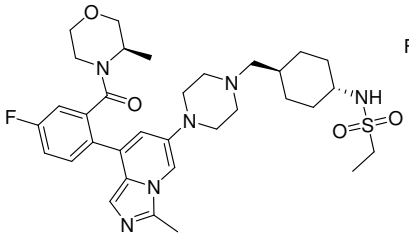

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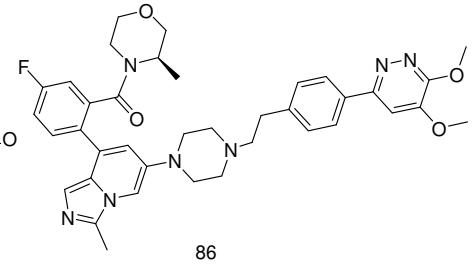

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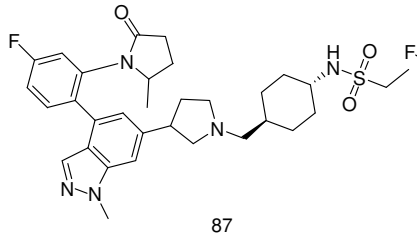

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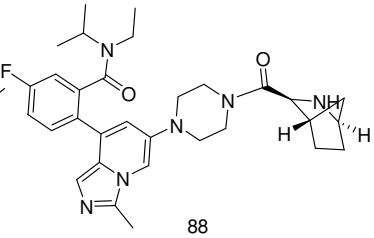

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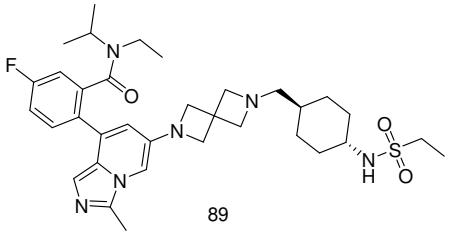

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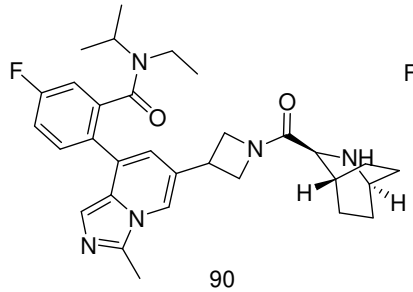

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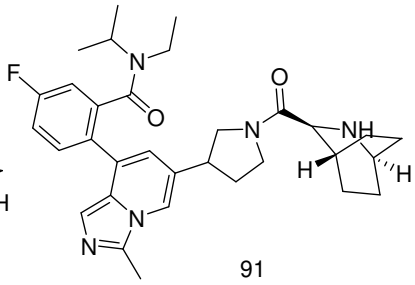

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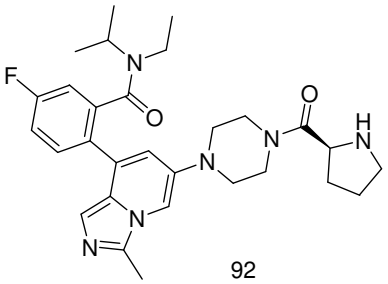

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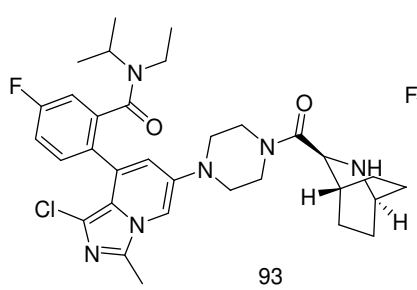

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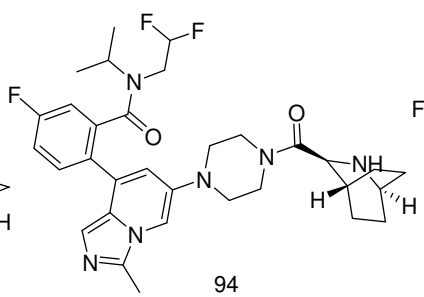

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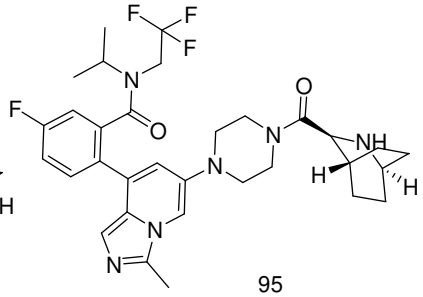

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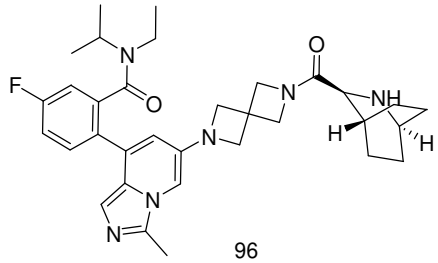

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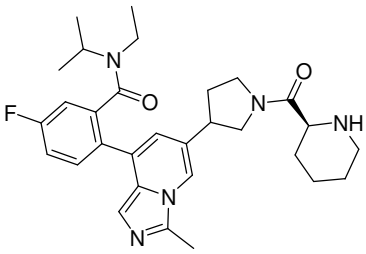

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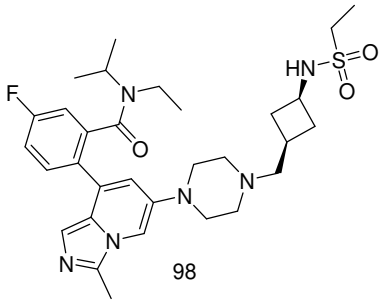

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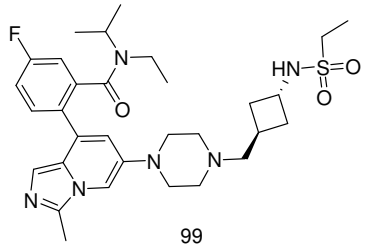

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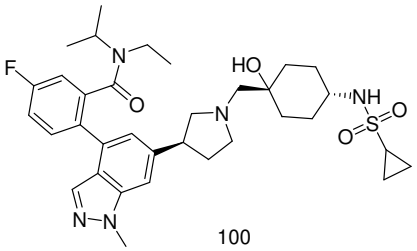

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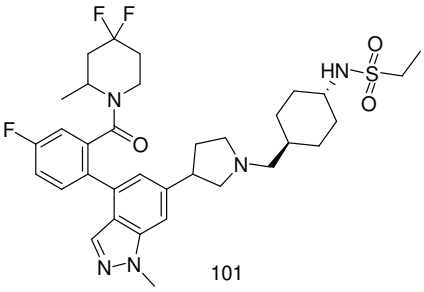

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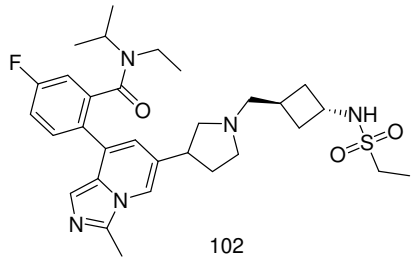

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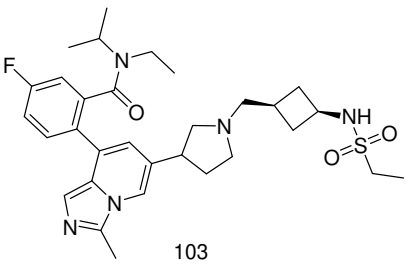

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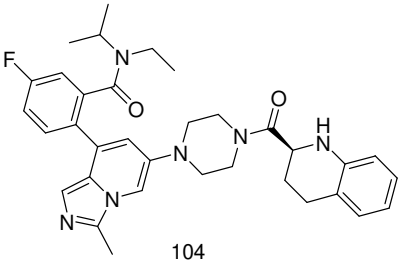

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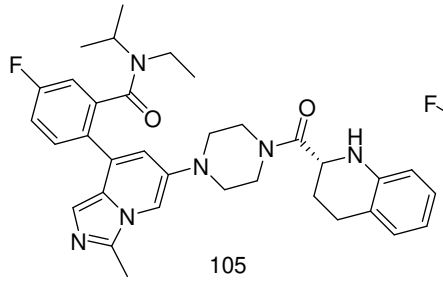

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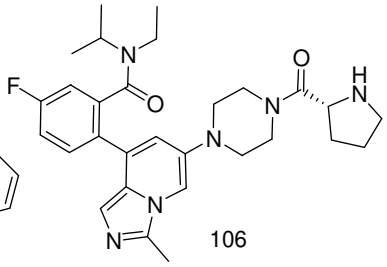

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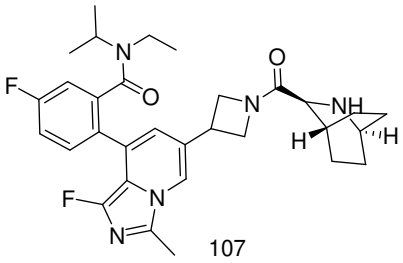

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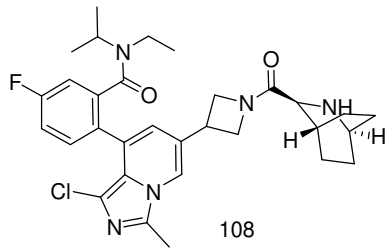

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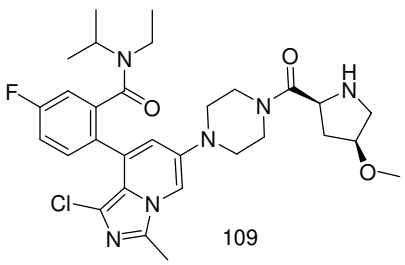

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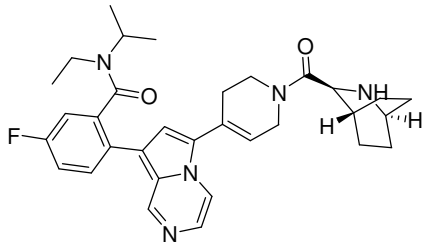

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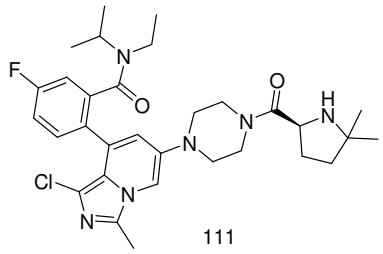

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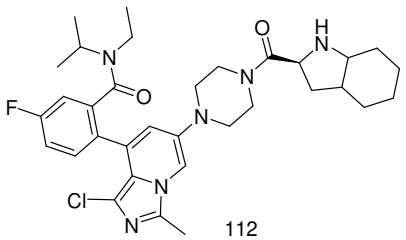

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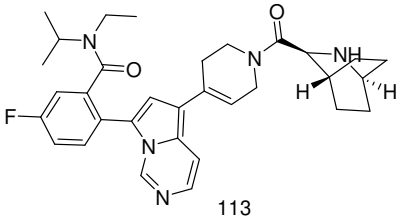

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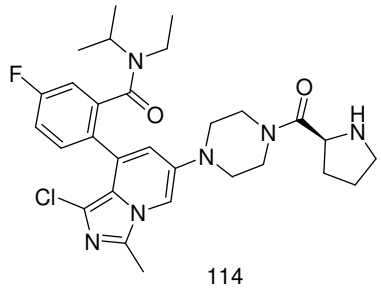

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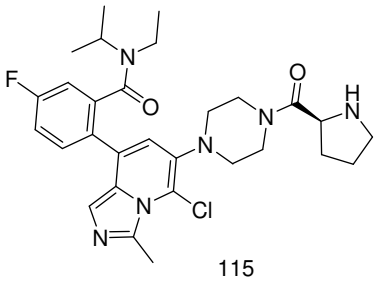

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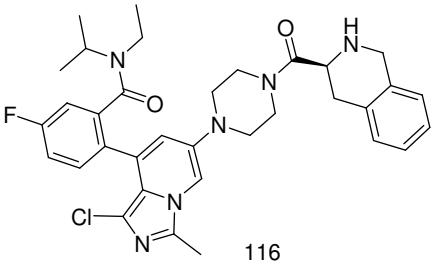

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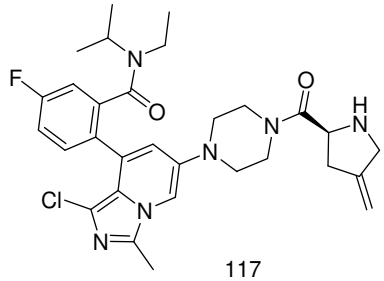

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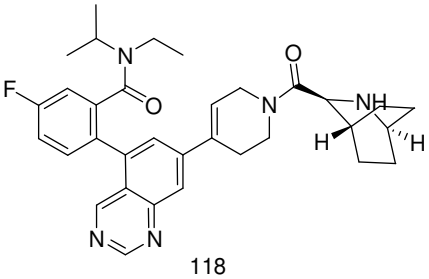

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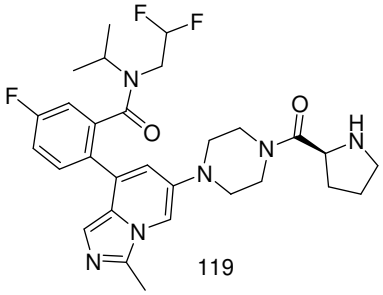

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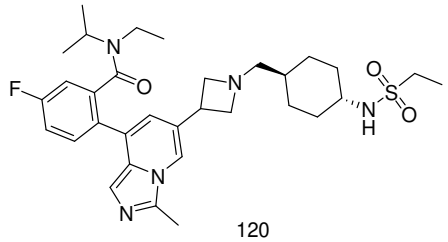

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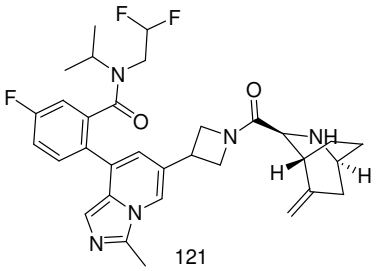

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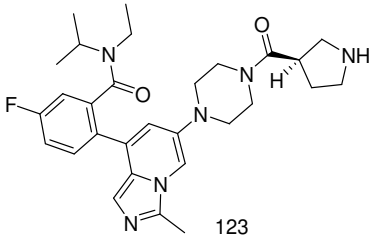

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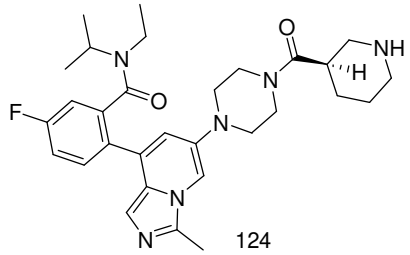

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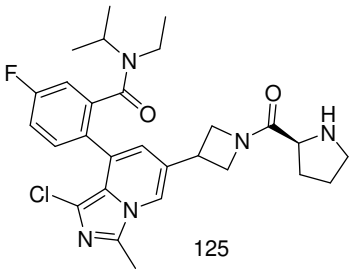

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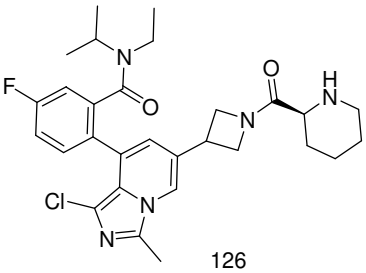

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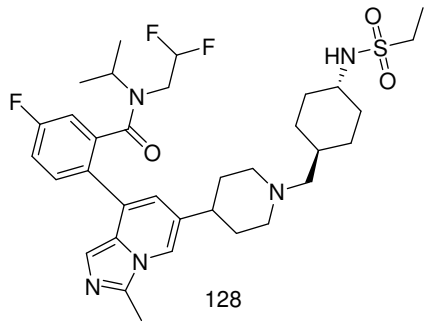

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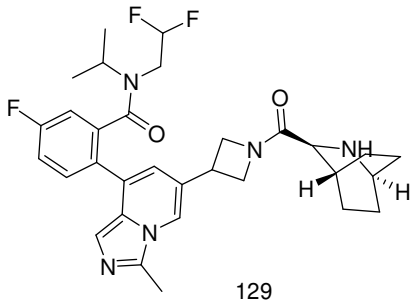

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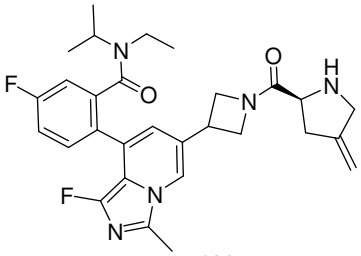

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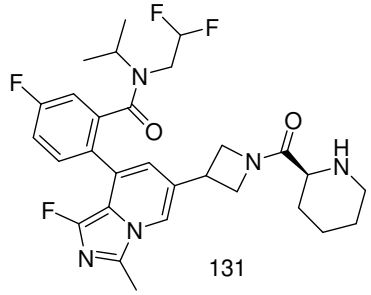

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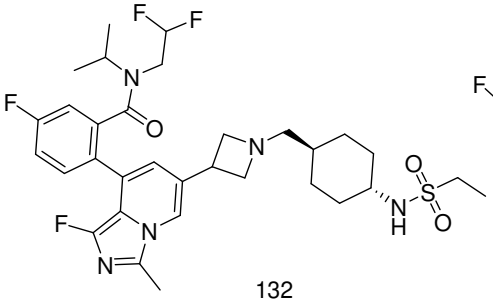

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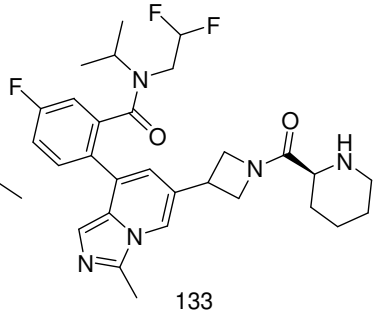

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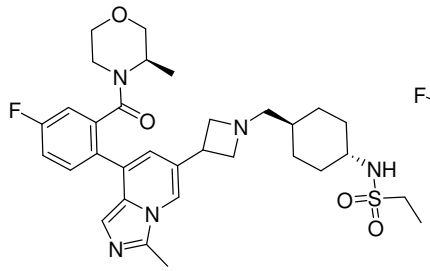

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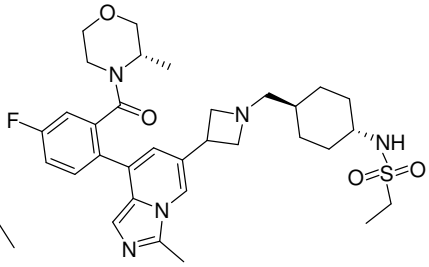

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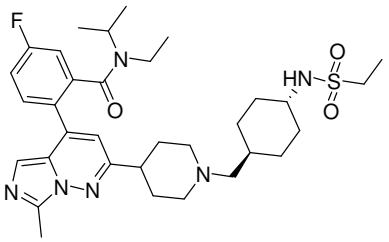

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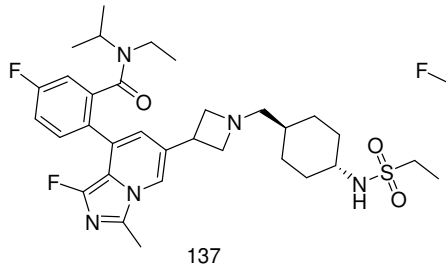

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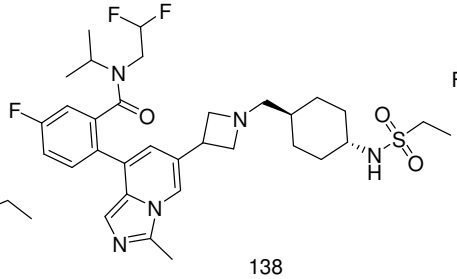

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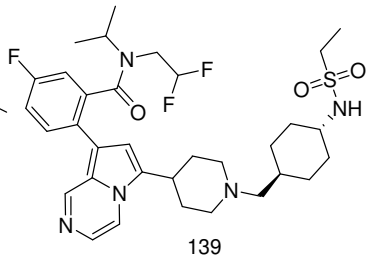

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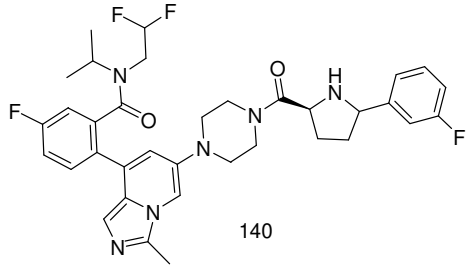

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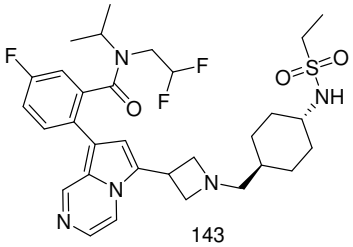

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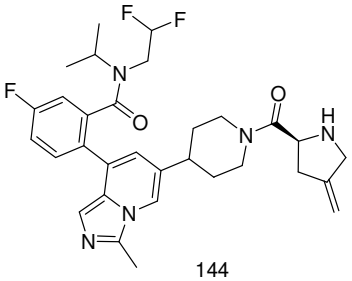

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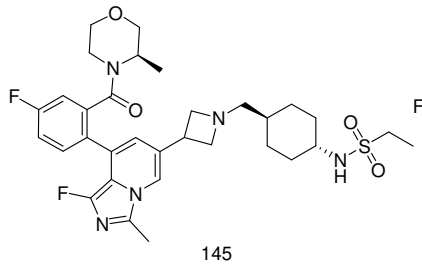

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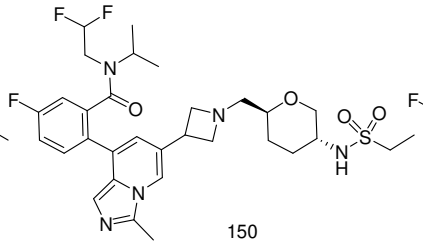

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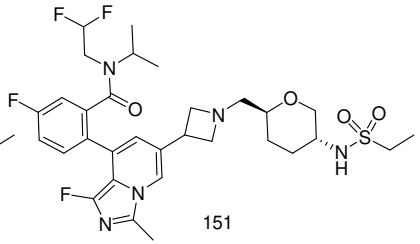

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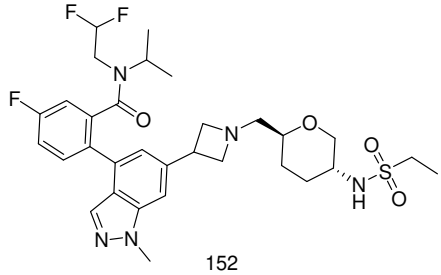

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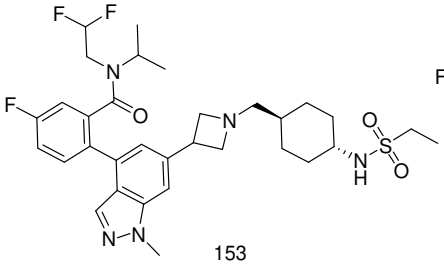

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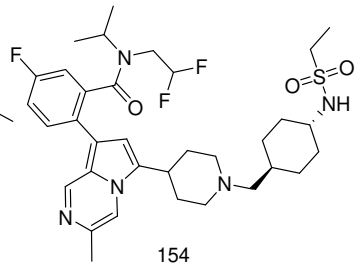

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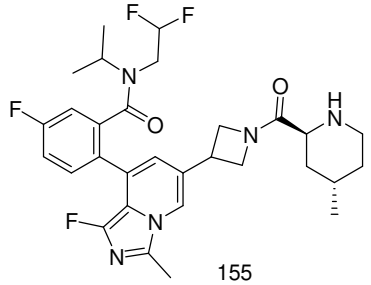

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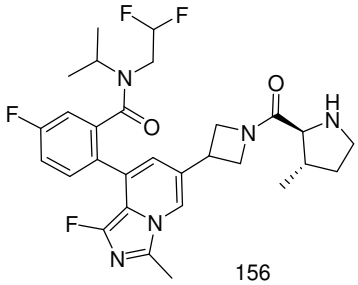

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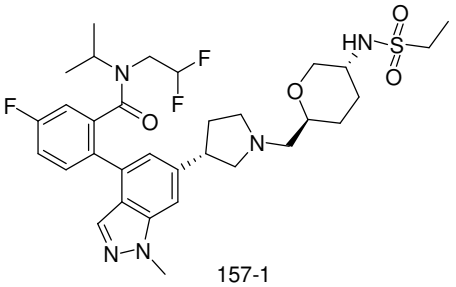
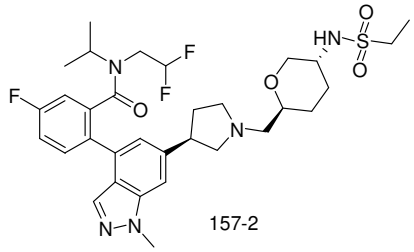


157-1



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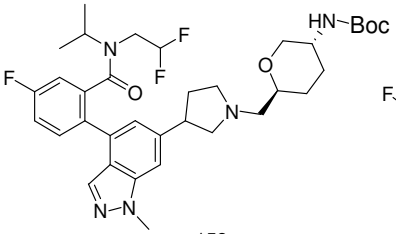

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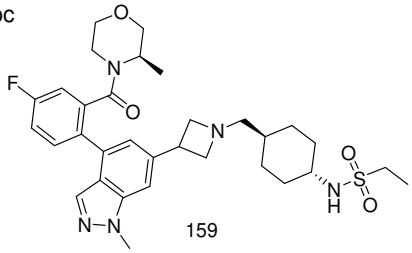

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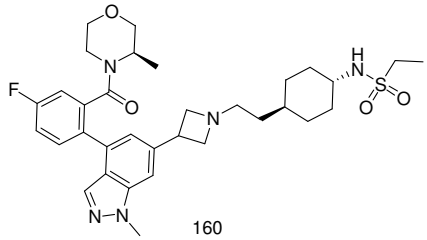

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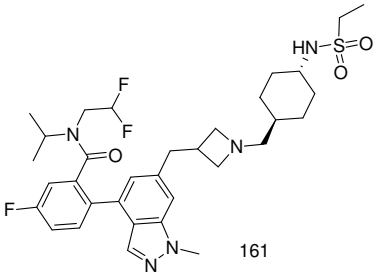

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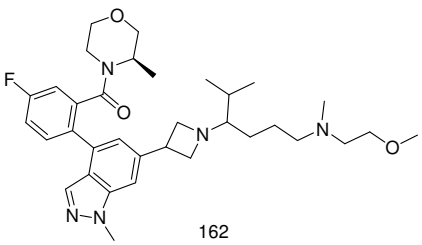

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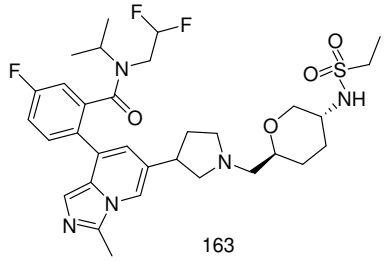

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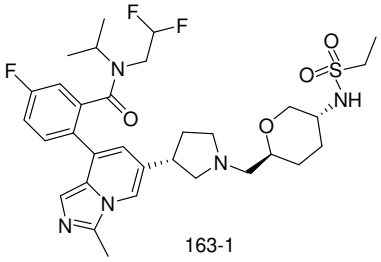

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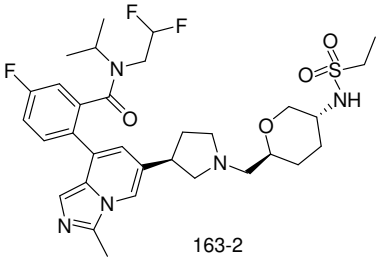

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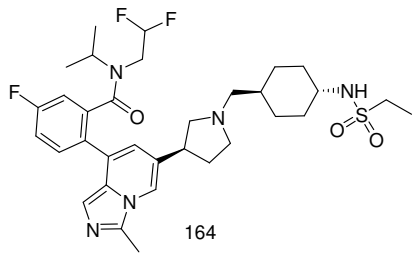

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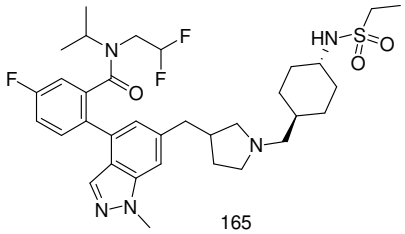

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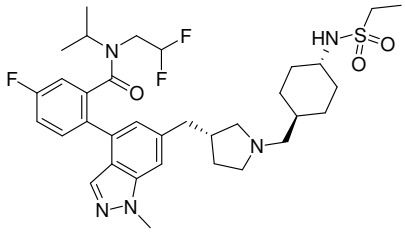

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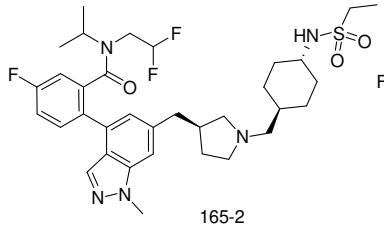

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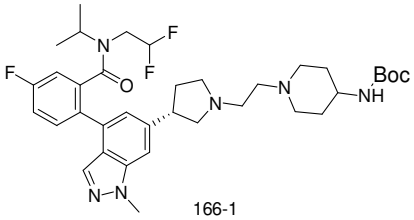

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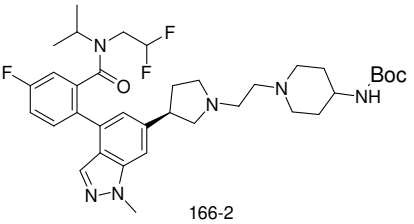

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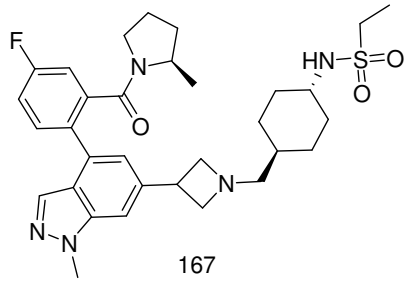

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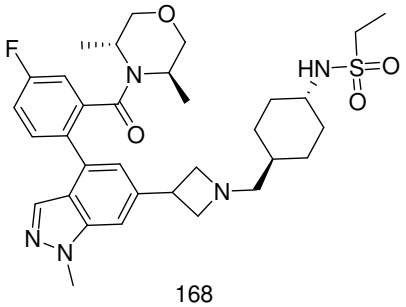

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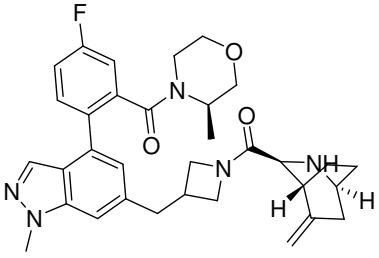

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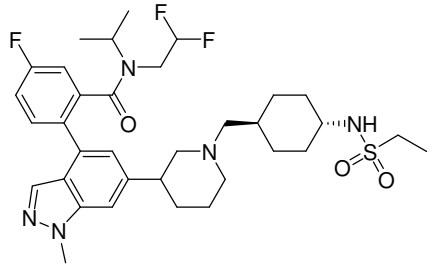

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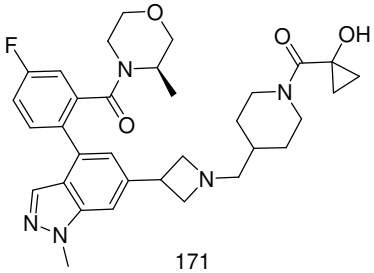

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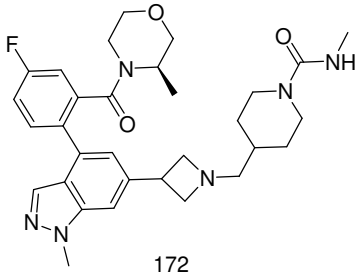

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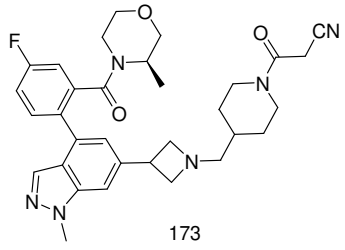

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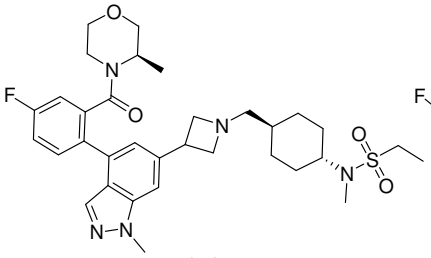

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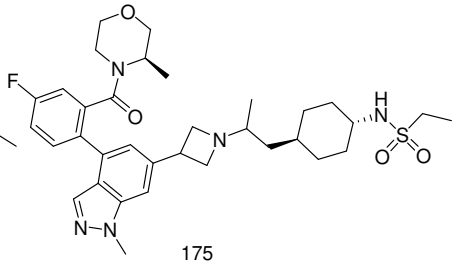

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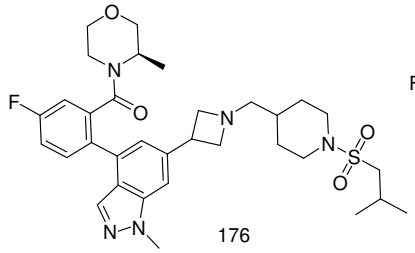

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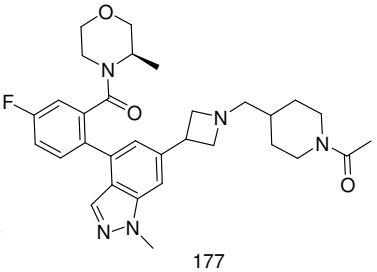

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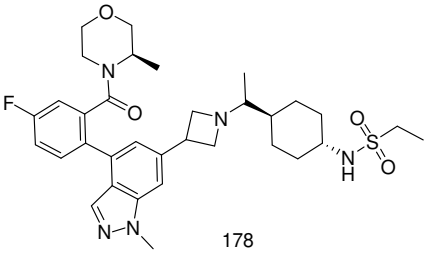

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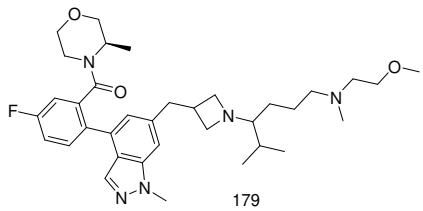

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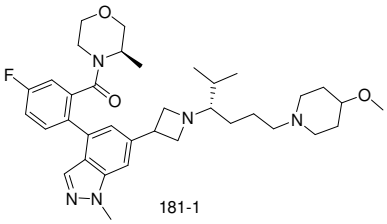

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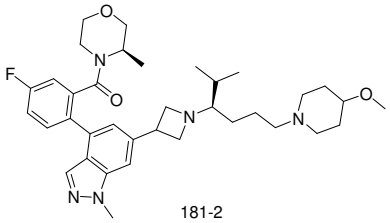

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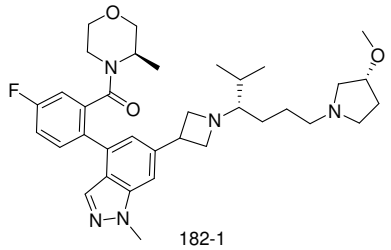

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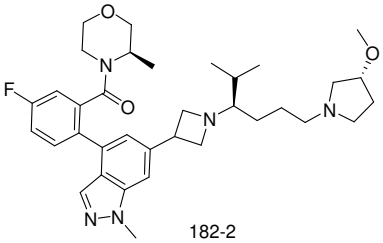

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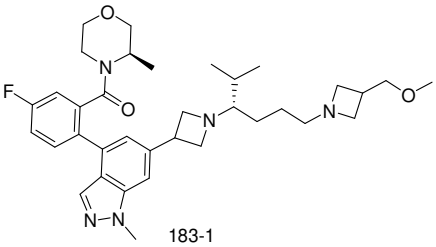

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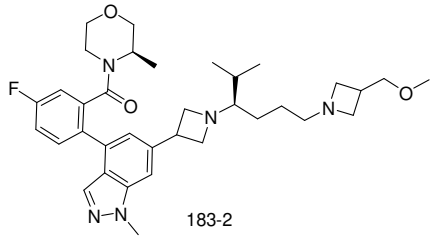

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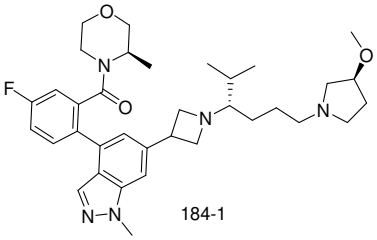

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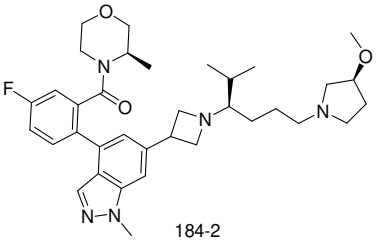

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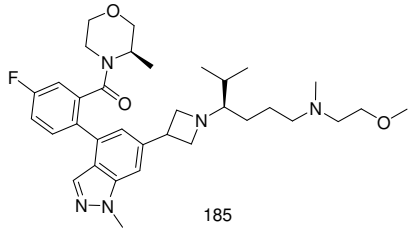

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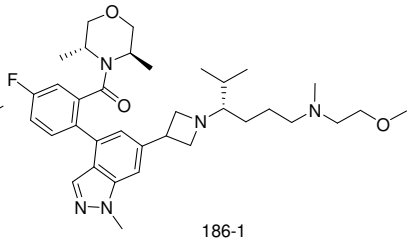

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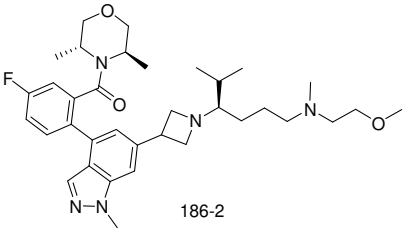
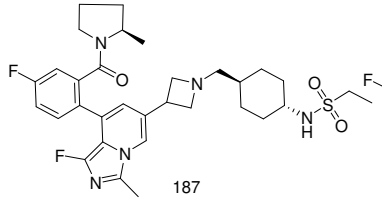


186-2



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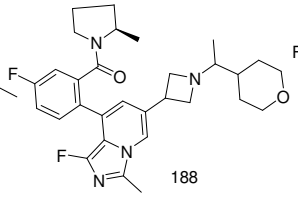

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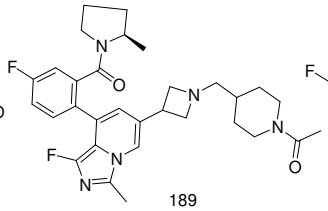

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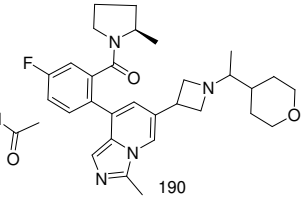

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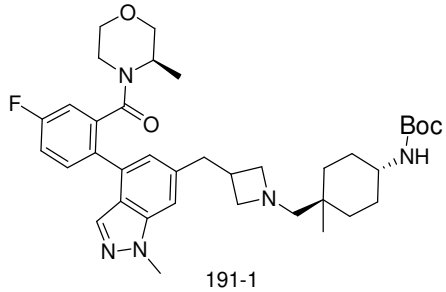

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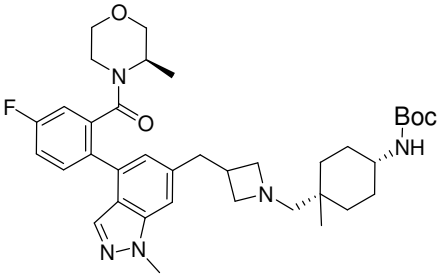
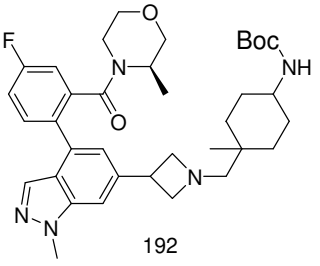


191-2



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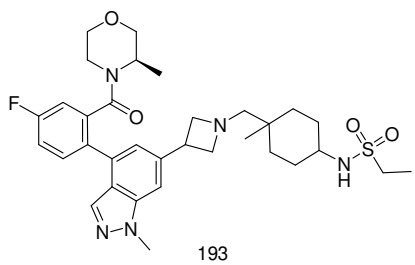

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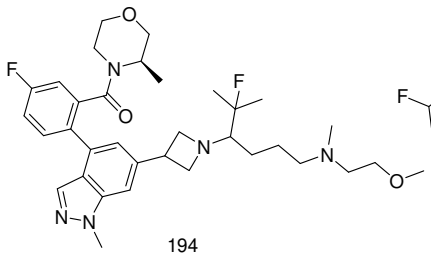

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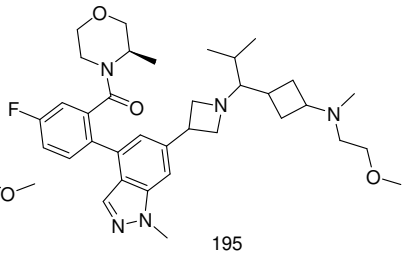

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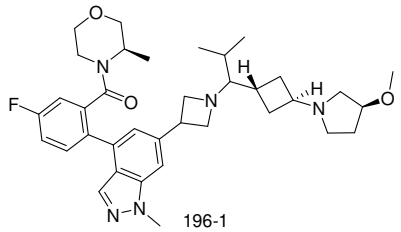
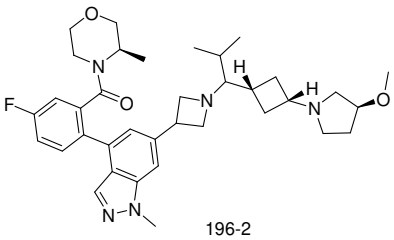


196-1



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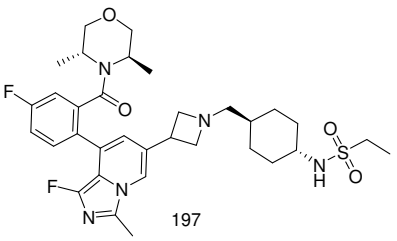

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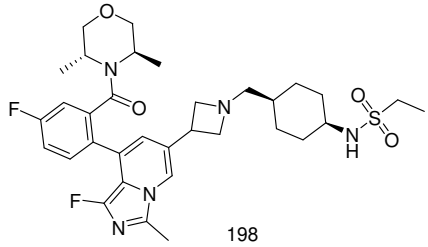

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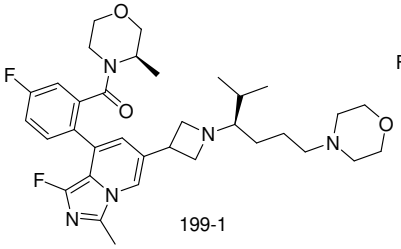

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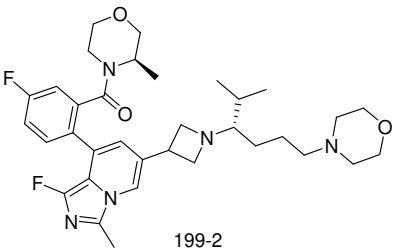

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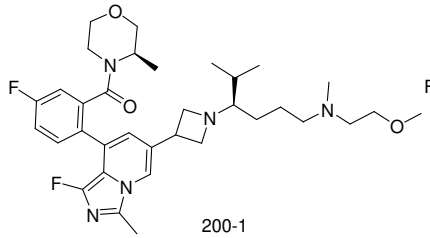

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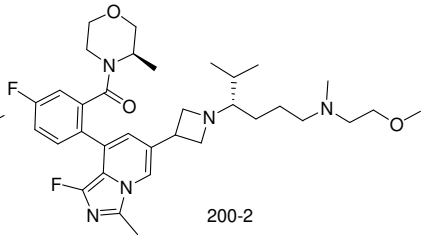
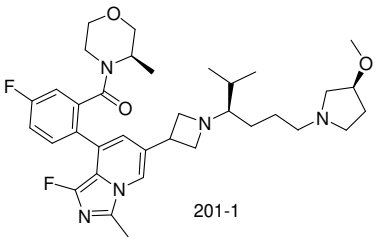
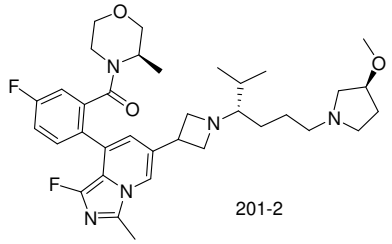


200-2



201-1



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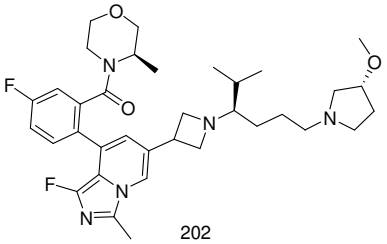

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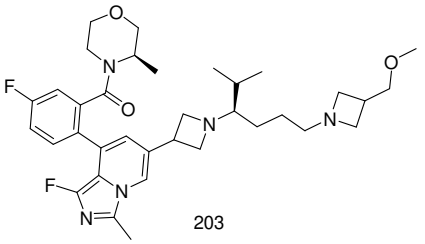

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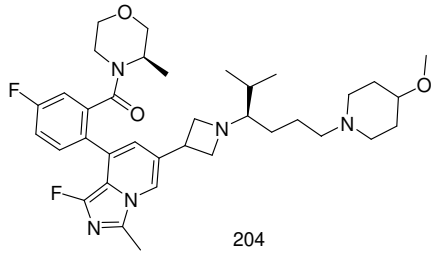

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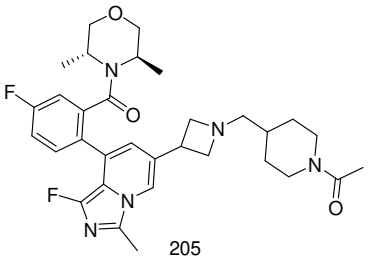

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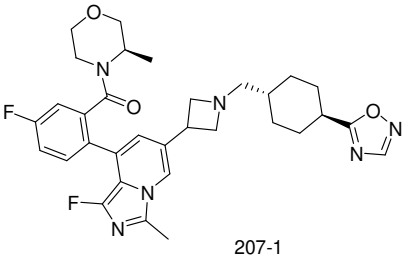
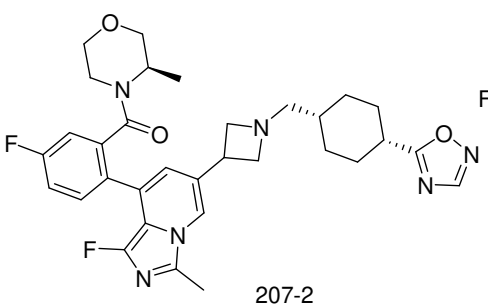


207-1



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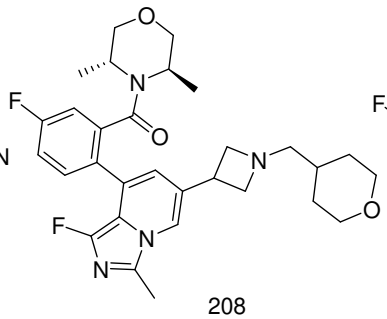

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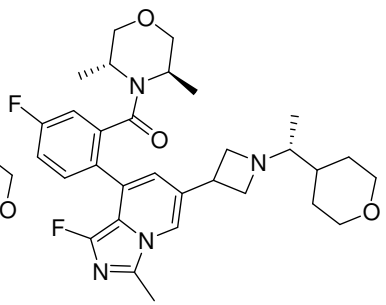

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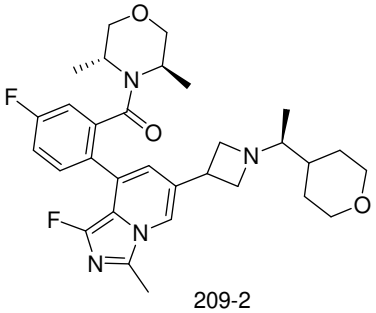

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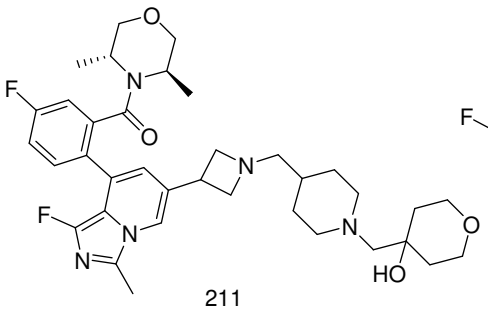

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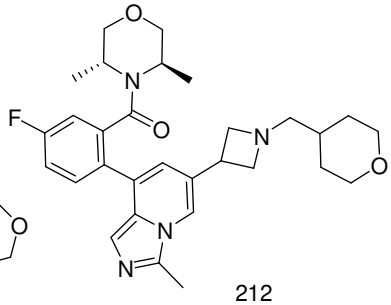

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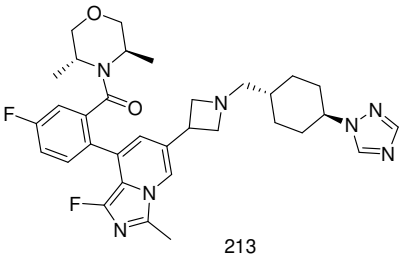

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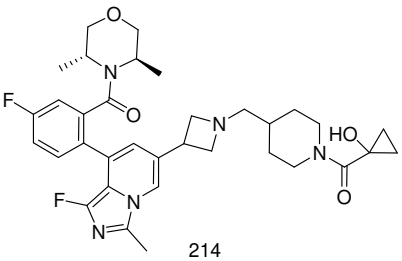

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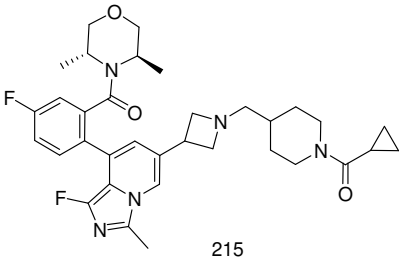

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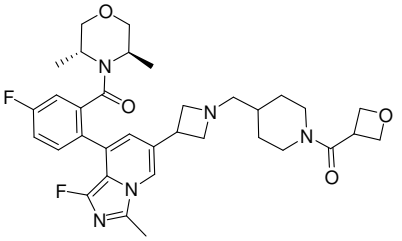

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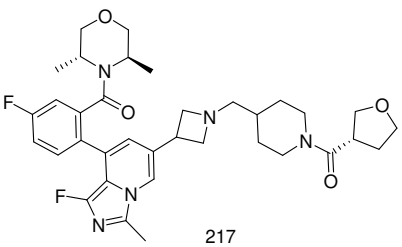

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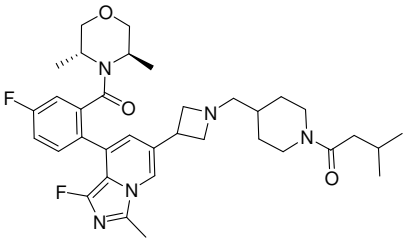

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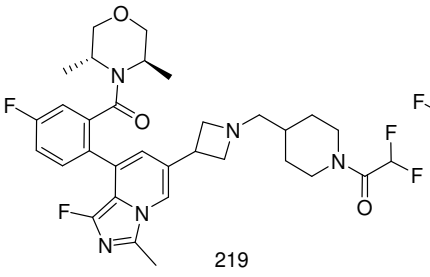

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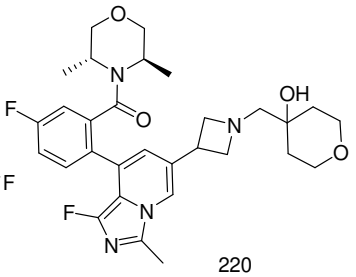

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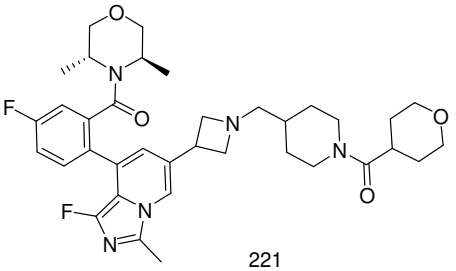

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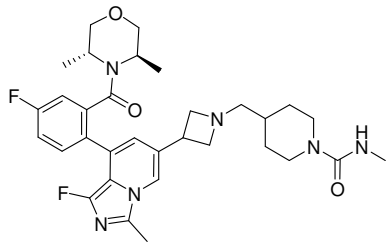

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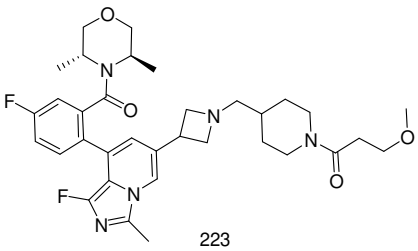

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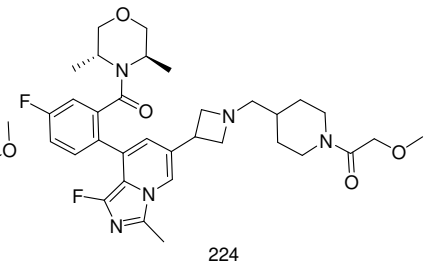

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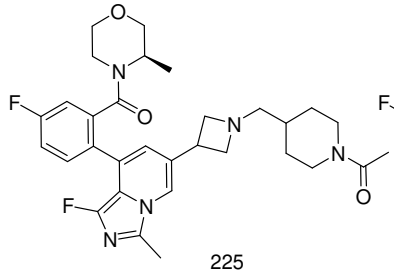

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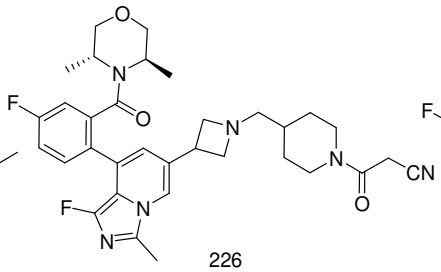

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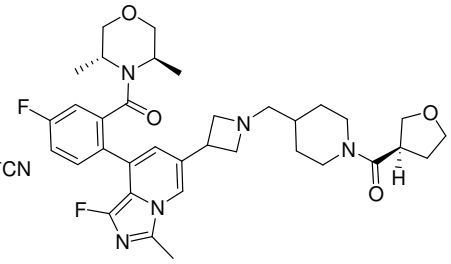

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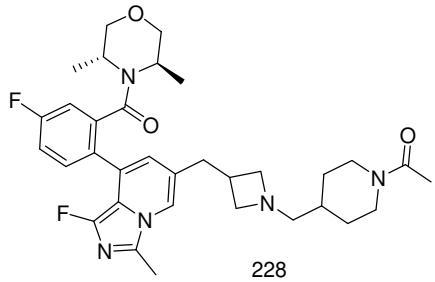

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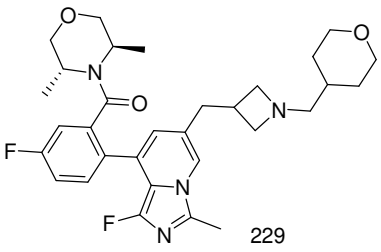

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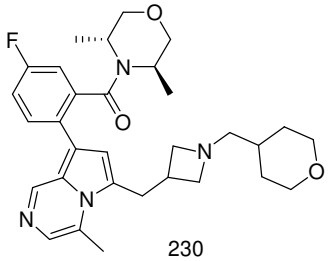

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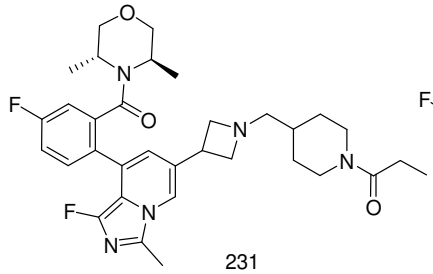

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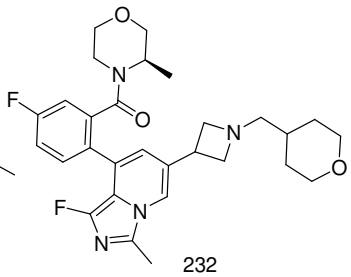

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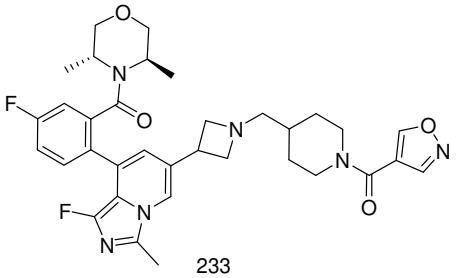

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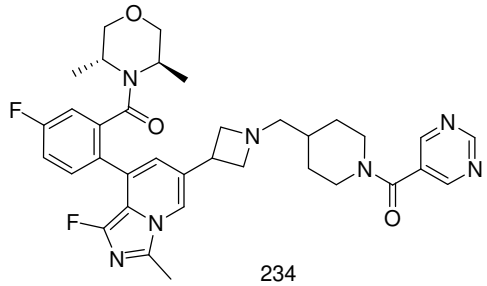

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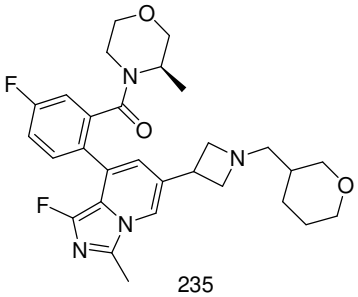

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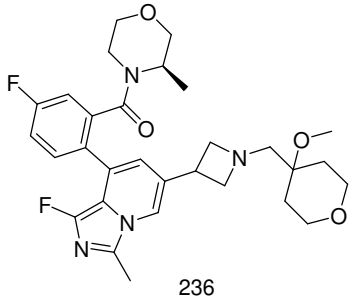

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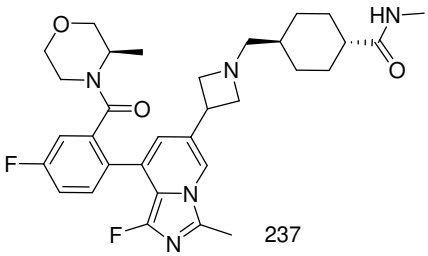

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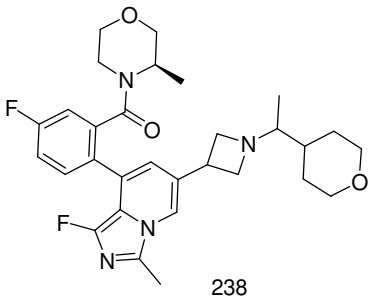

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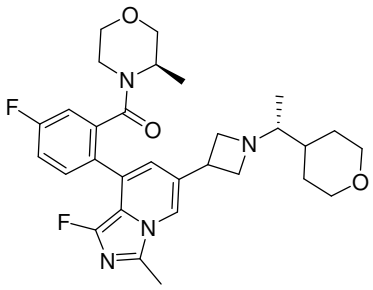

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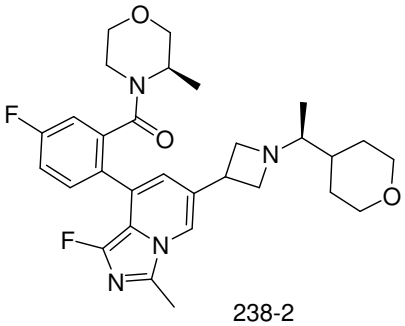

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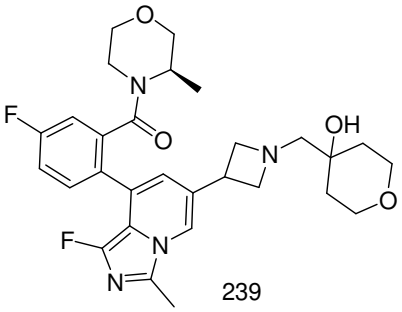

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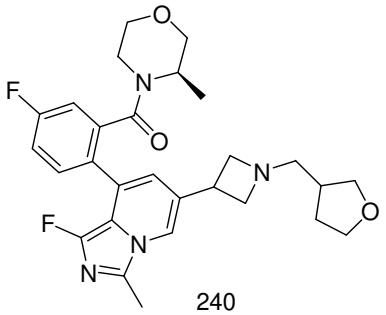

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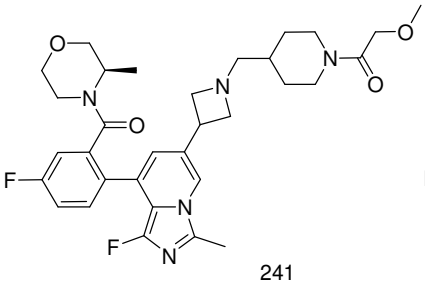

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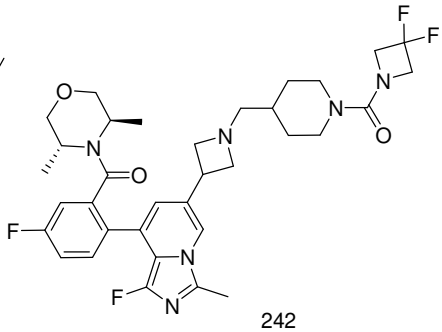

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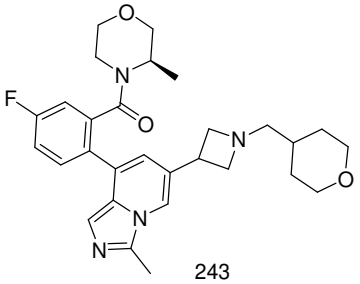

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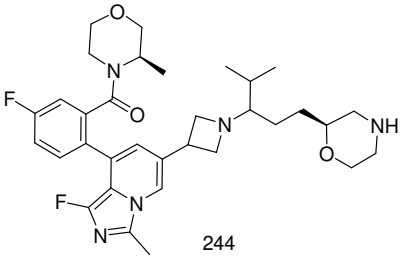

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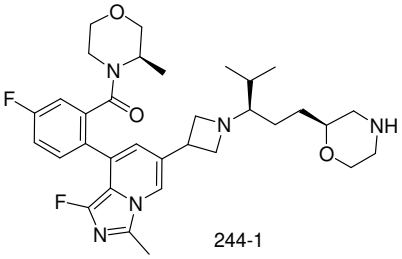
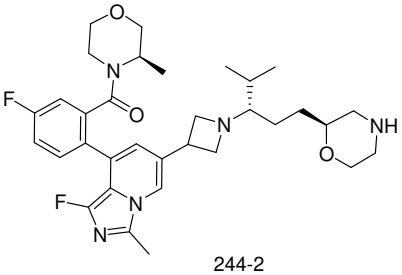


244-1



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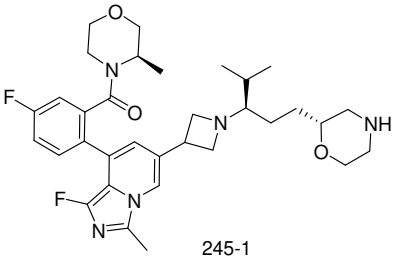

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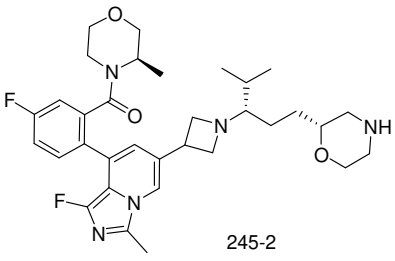

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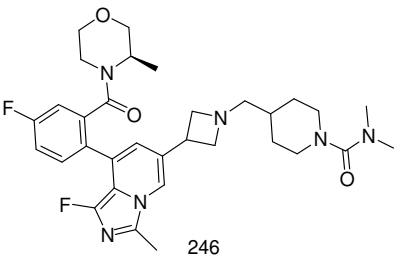

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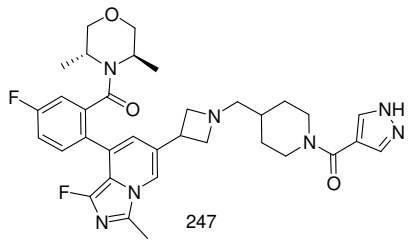

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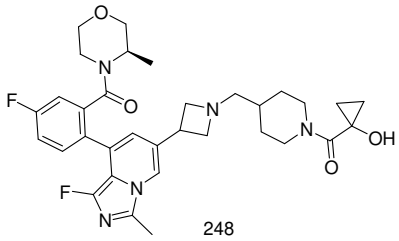

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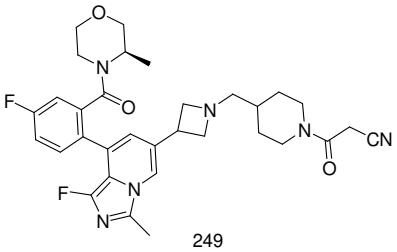

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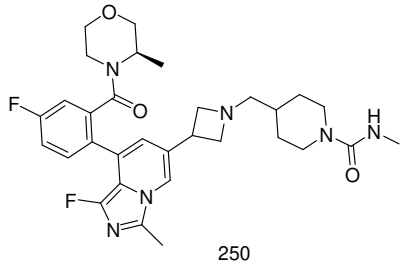

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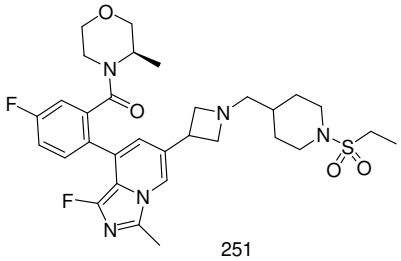

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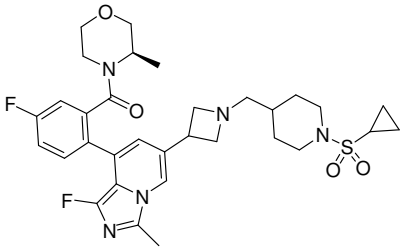

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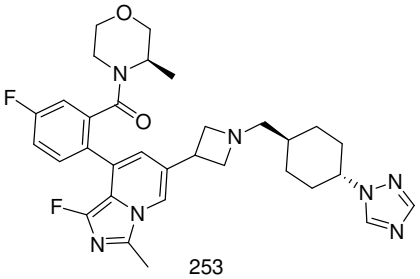

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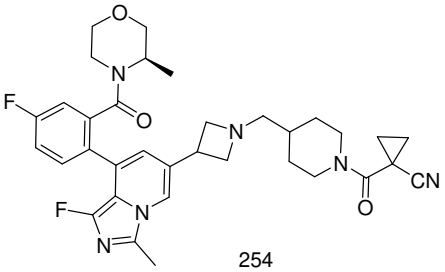

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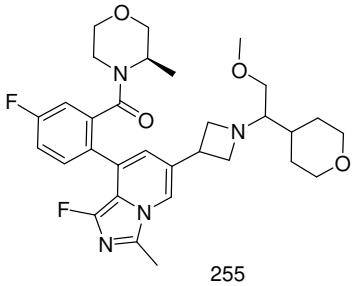

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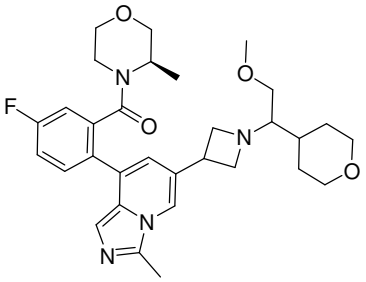

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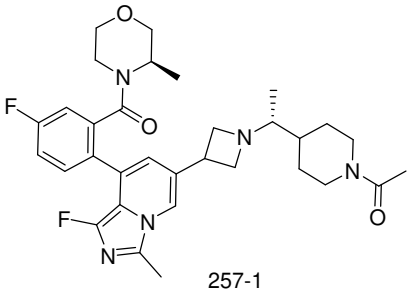

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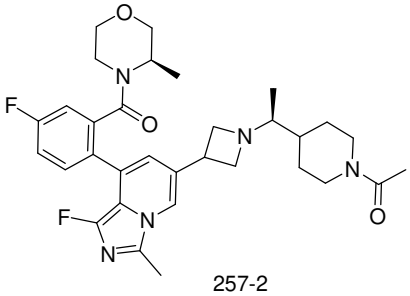

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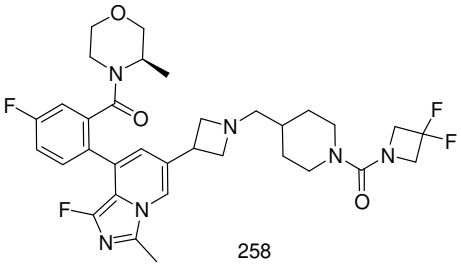

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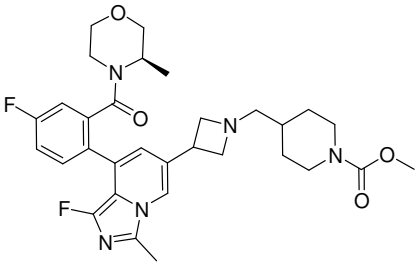

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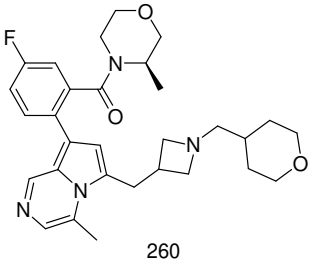

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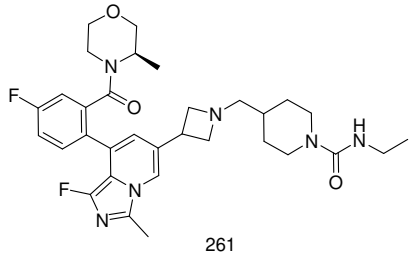

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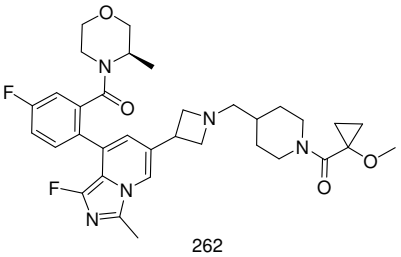

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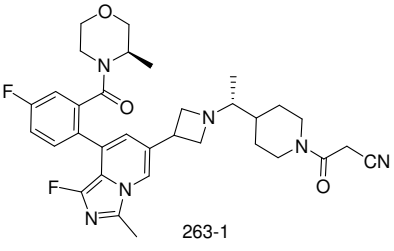

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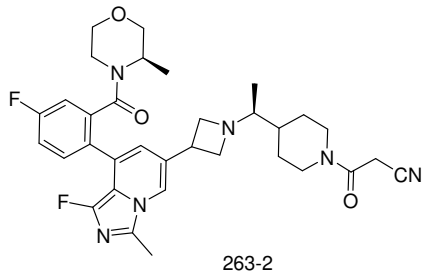

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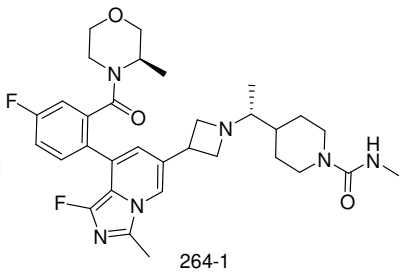

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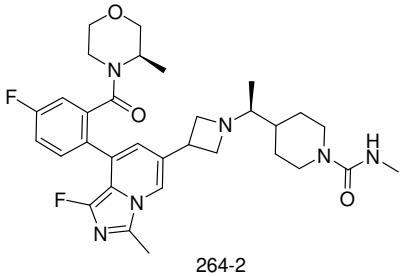

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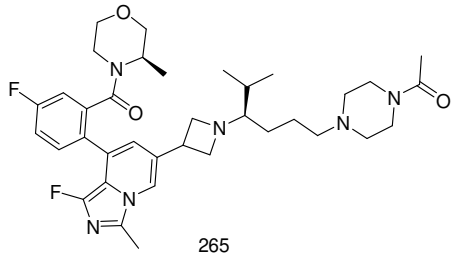

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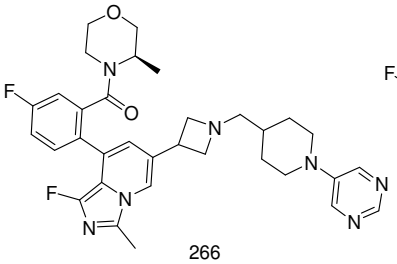

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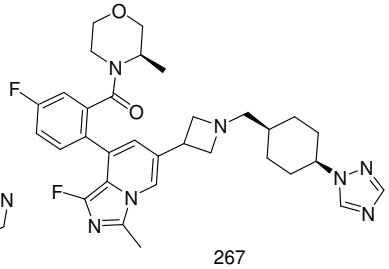

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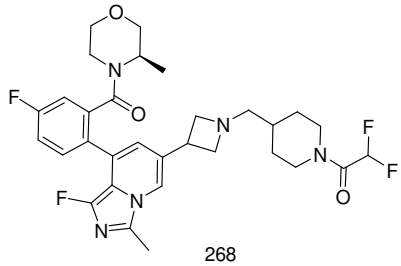

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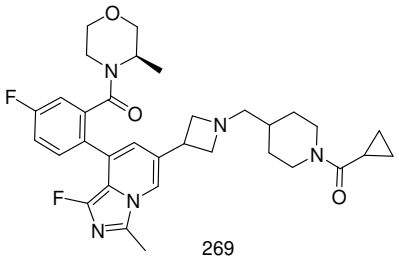

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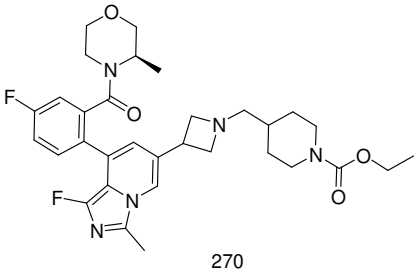

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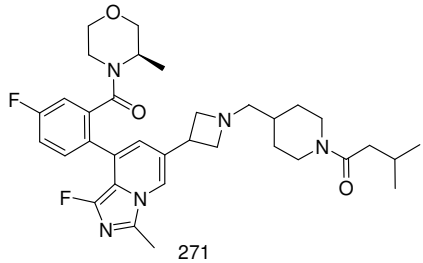

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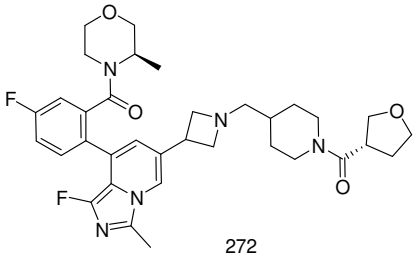

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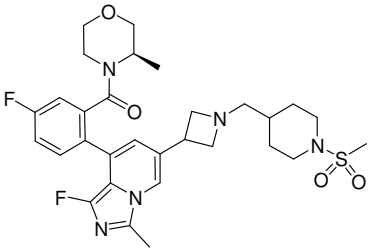

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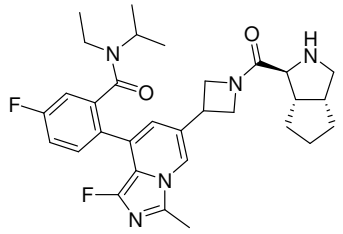

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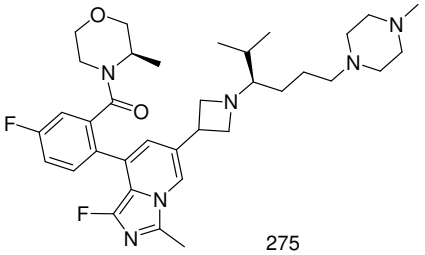

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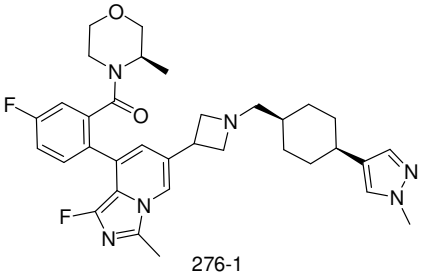

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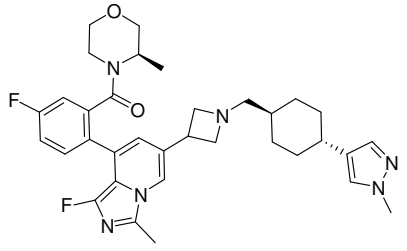

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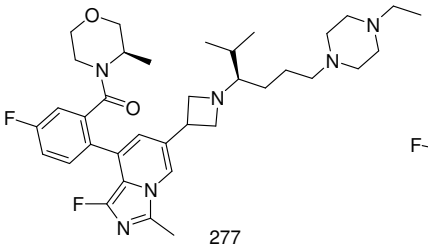

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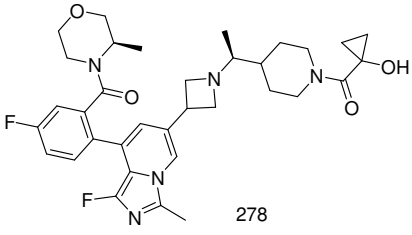

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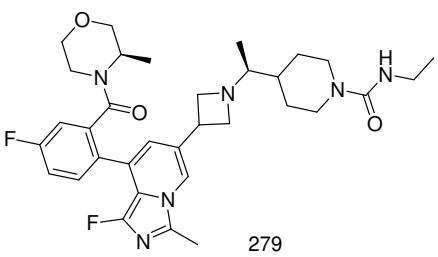

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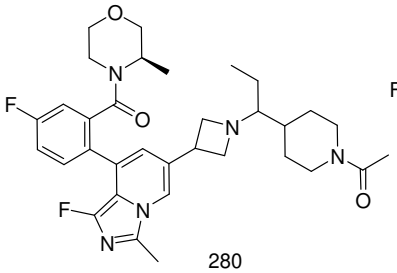

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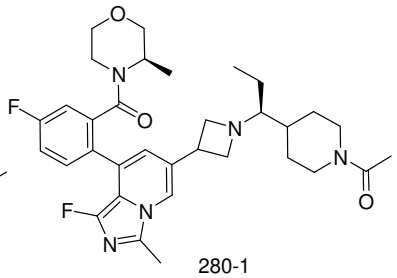

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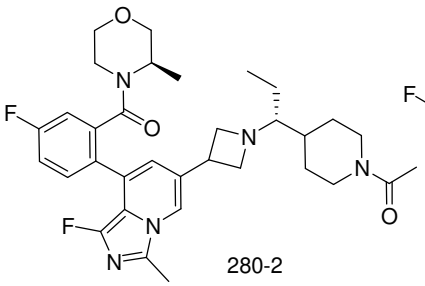

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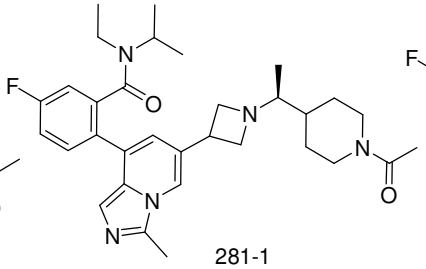

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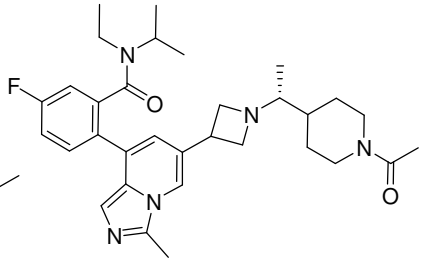

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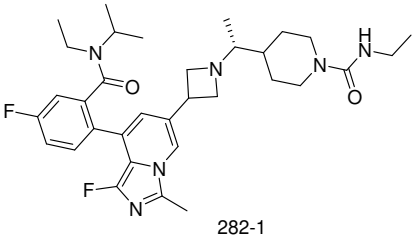

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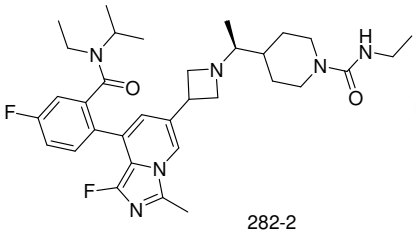

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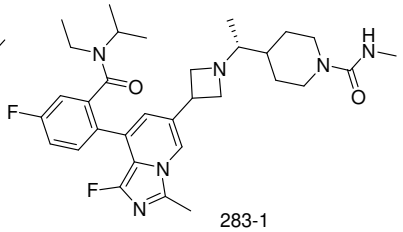

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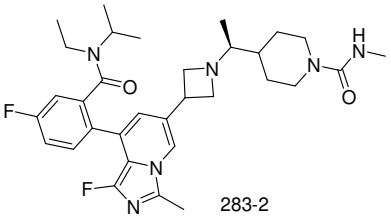

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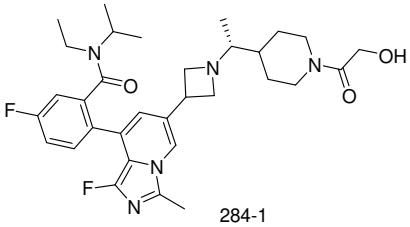

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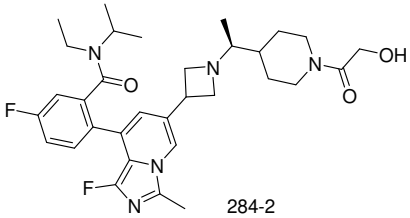

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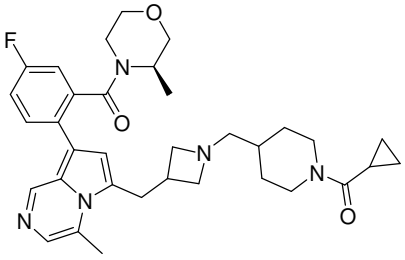

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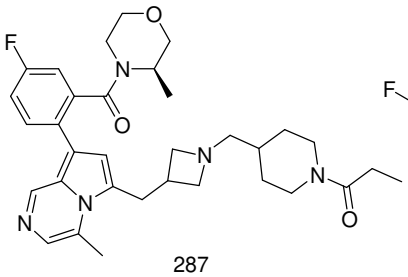

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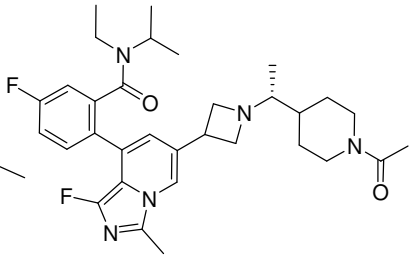

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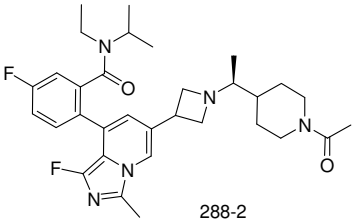

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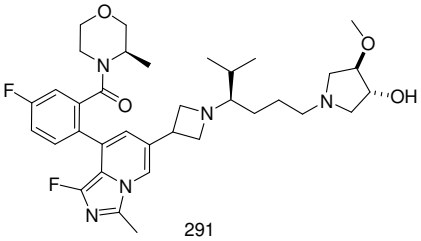

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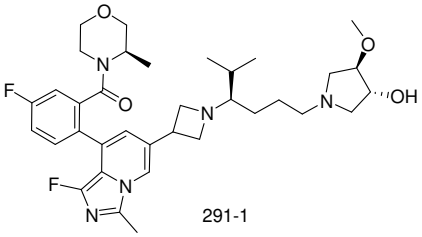

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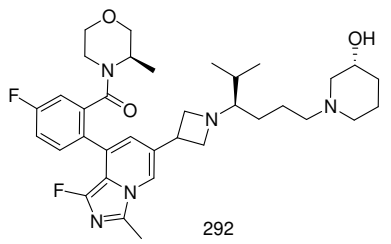

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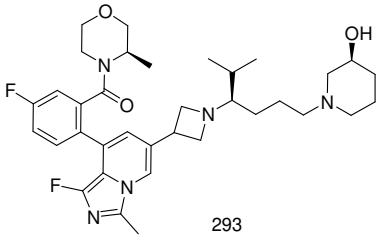

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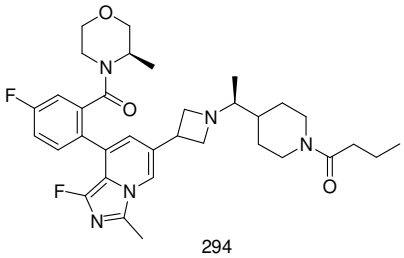

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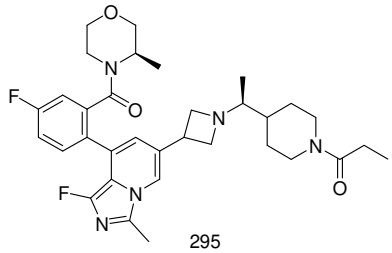

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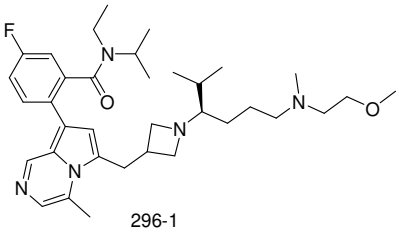

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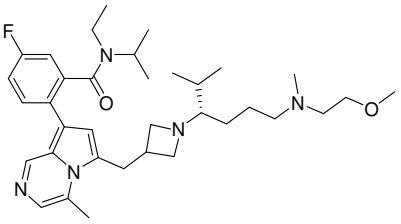

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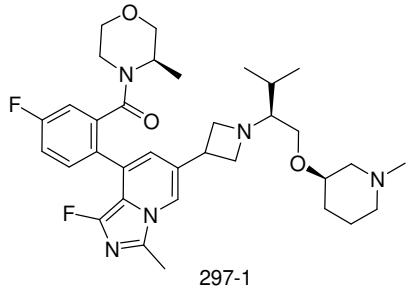

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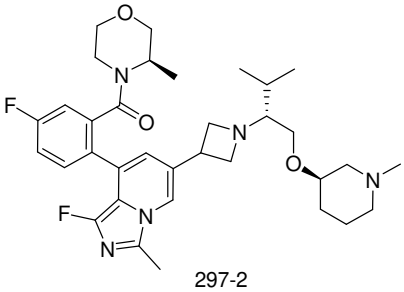

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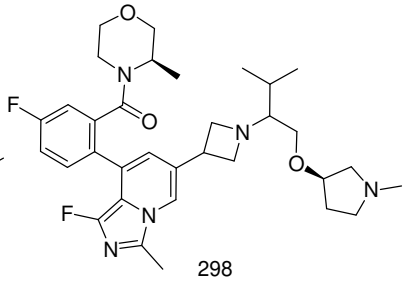

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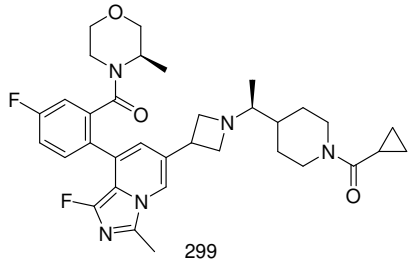

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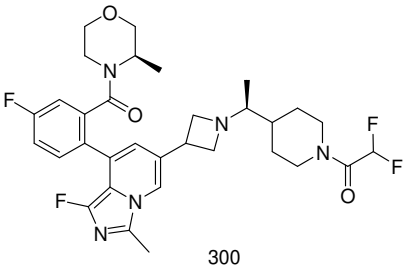

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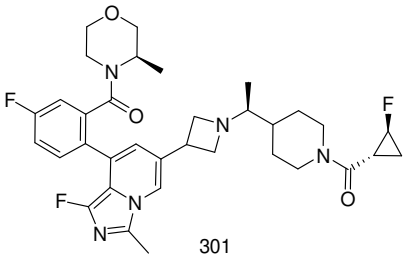

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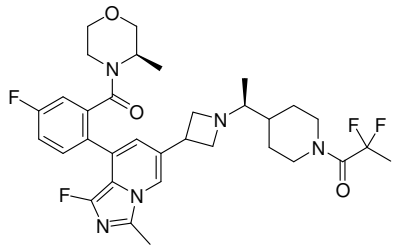

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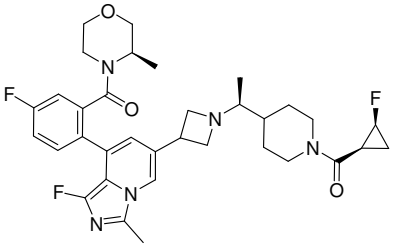

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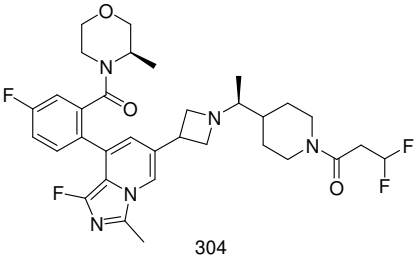

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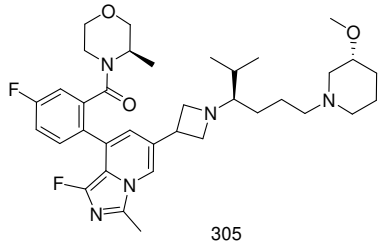

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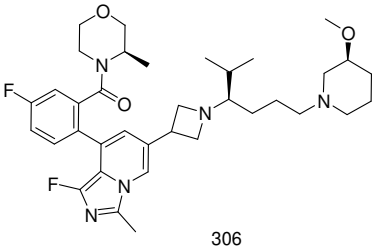

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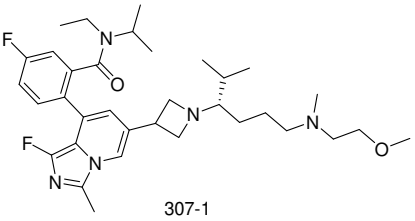

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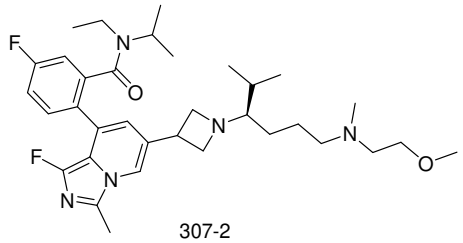

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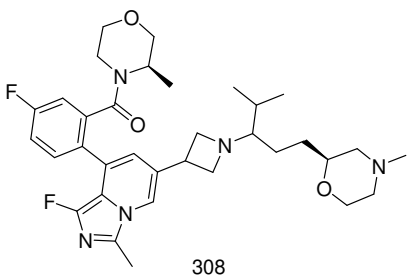

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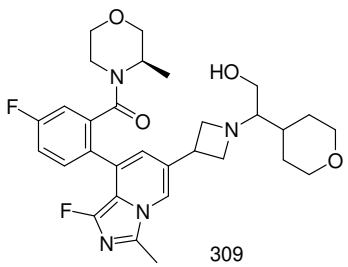

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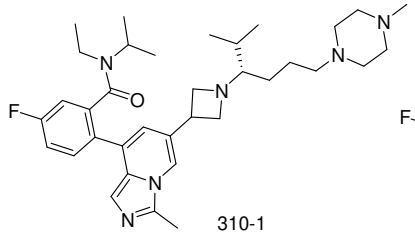

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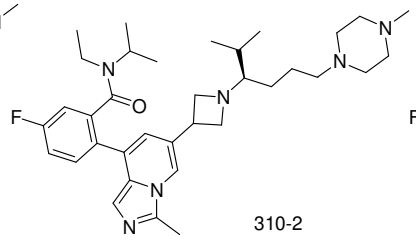

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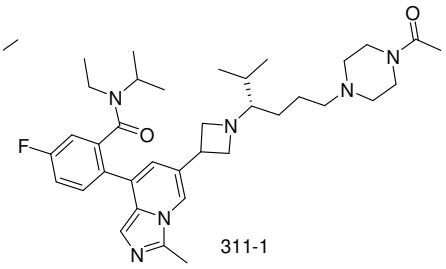

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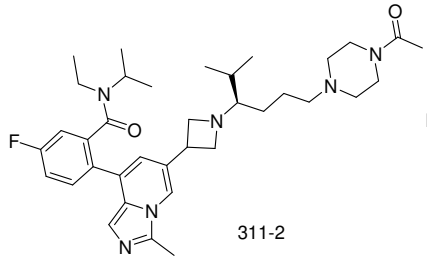

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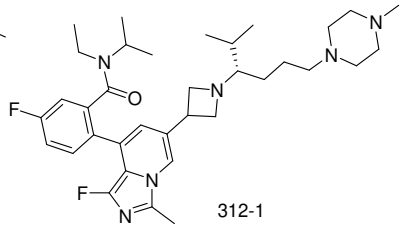

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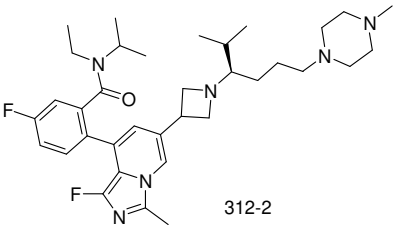

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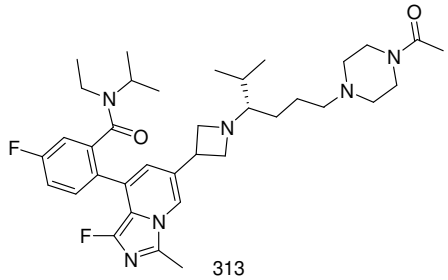

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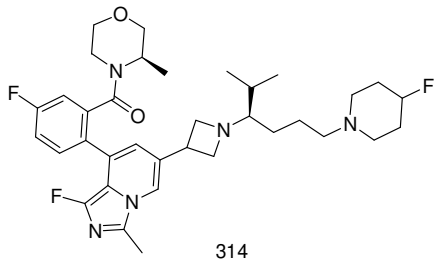

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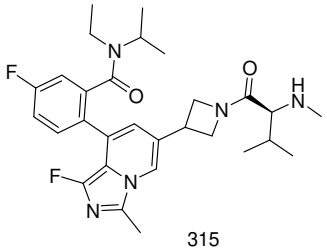

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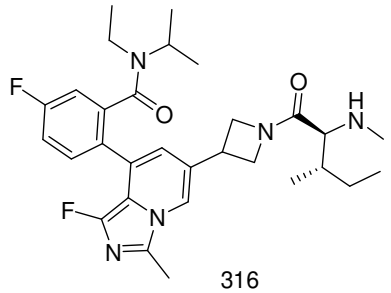

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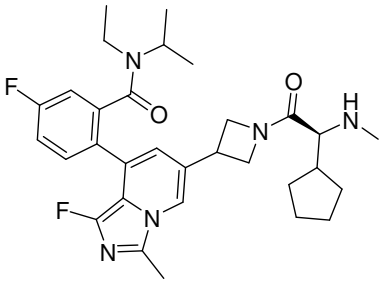

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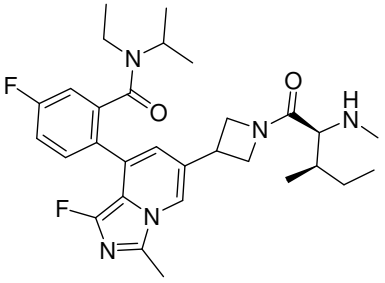

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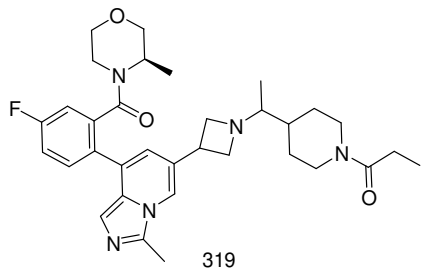

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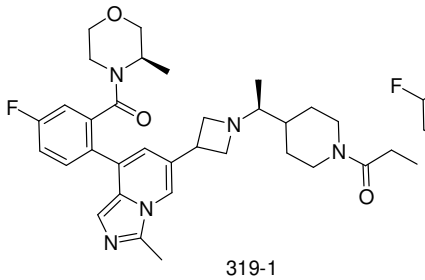

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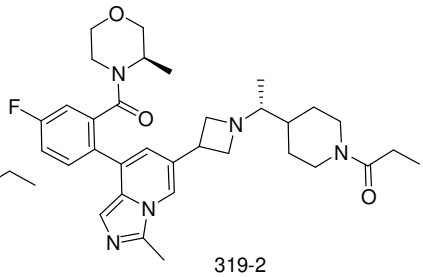

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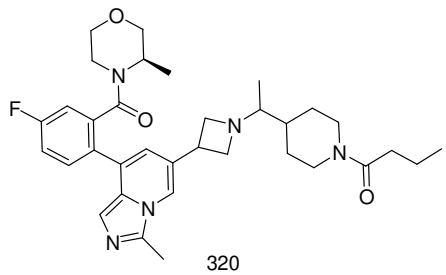

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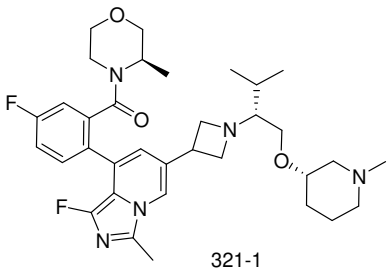

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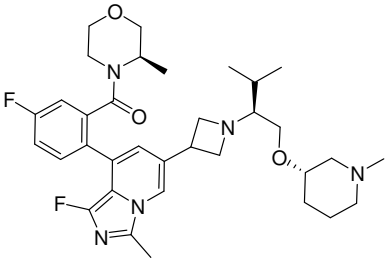

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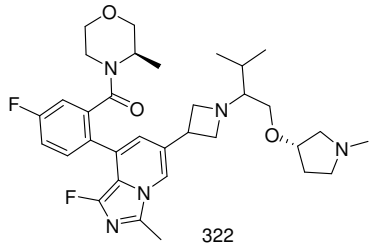

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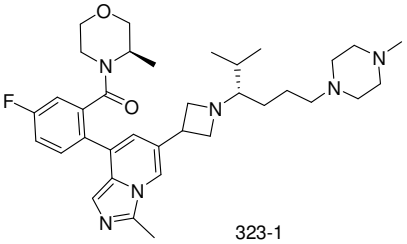

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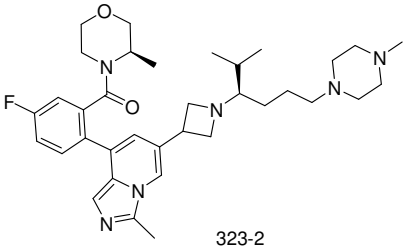

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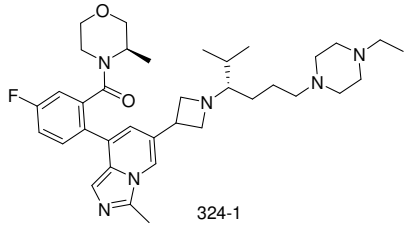

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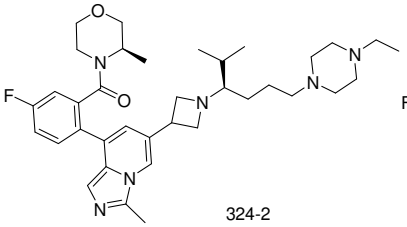

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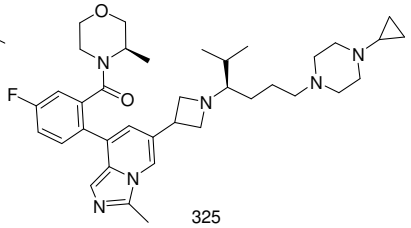

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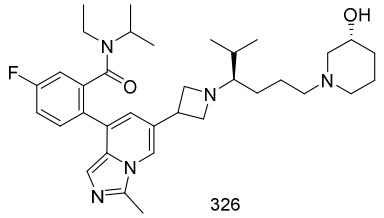

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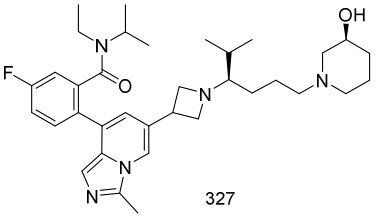

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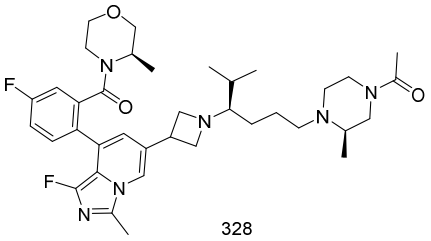

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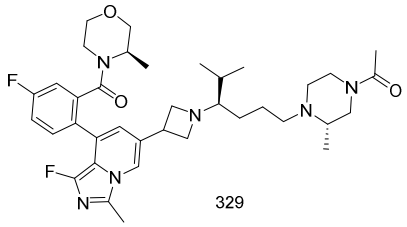

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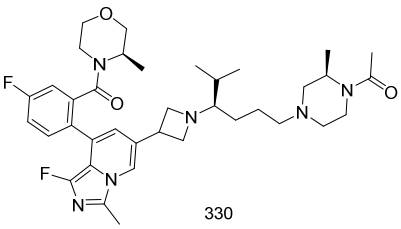

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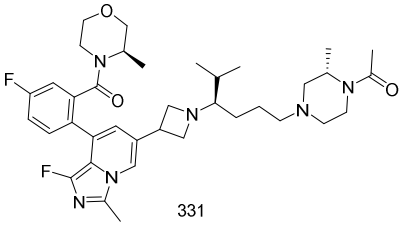

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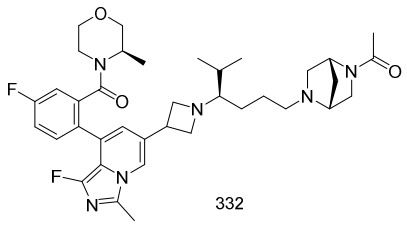

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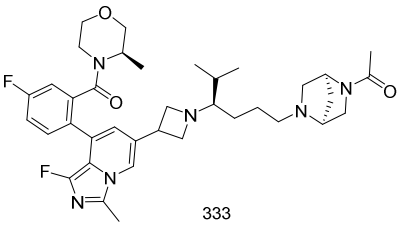

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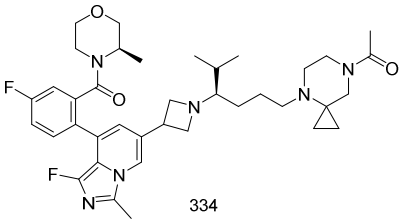

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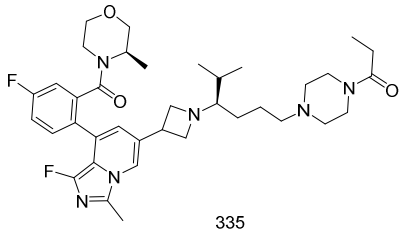

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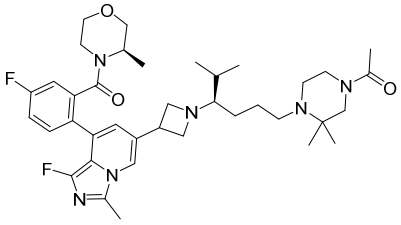

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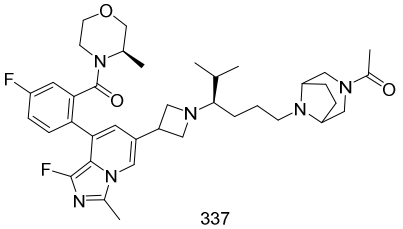

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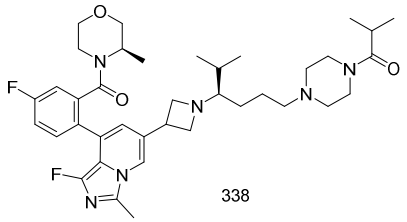

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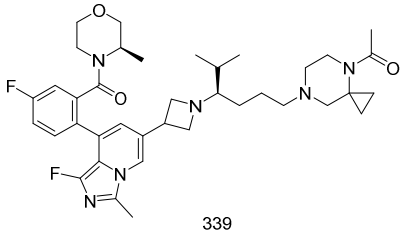

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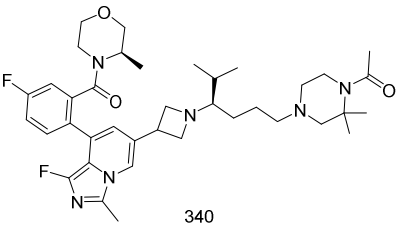

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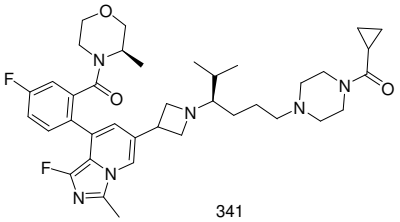

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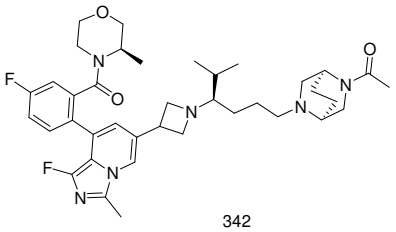

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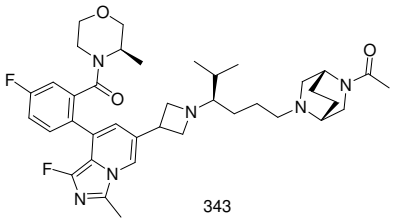

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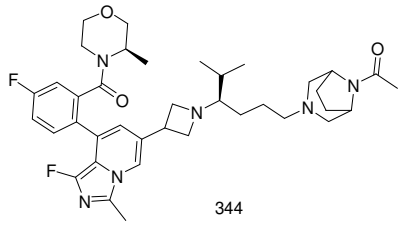

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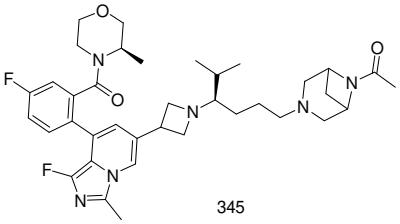

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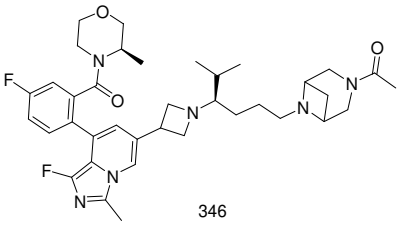

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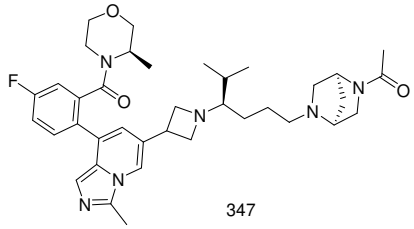

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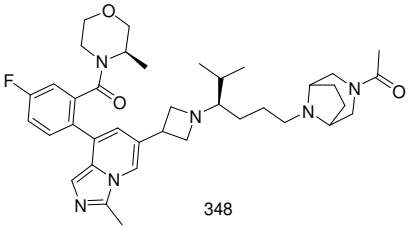

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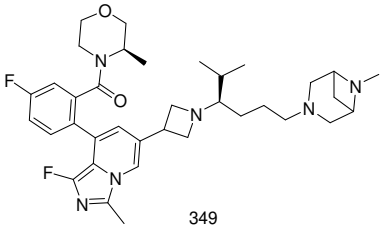

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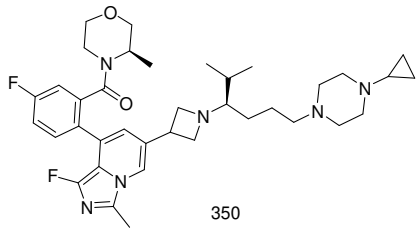

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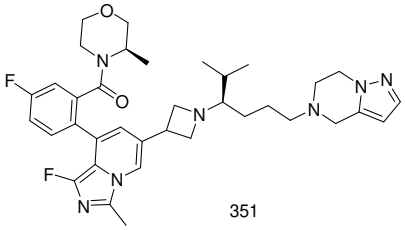

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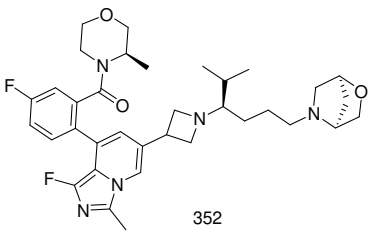

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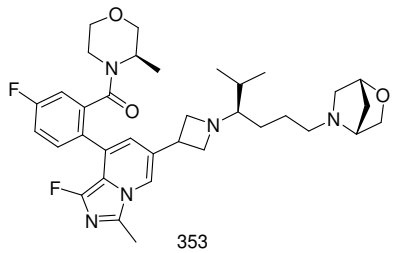

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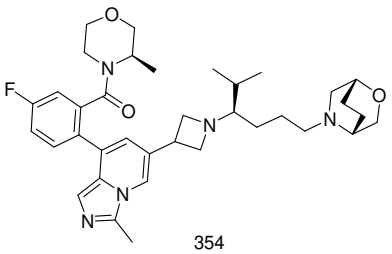

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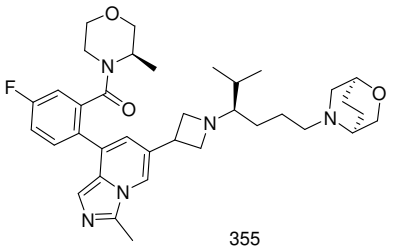

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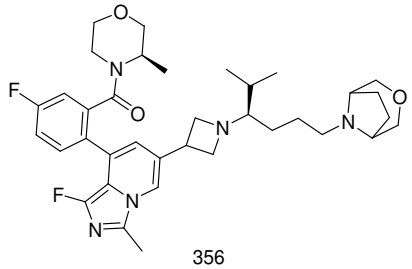

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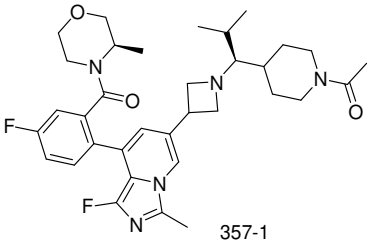
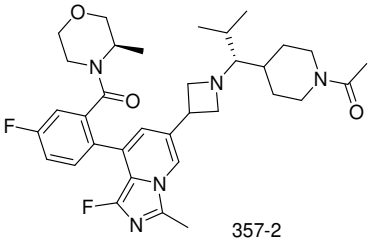


357-1



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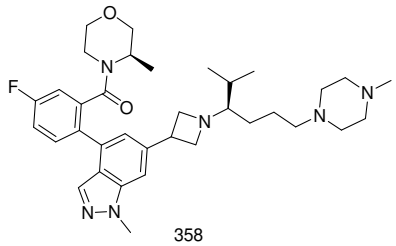

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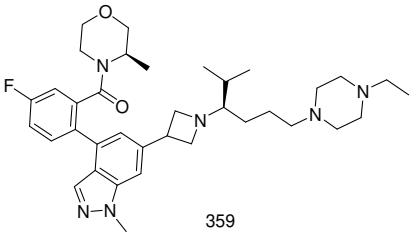

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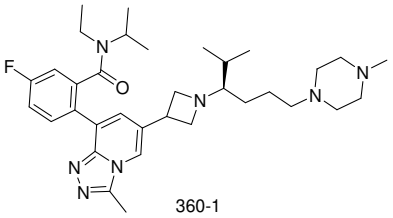

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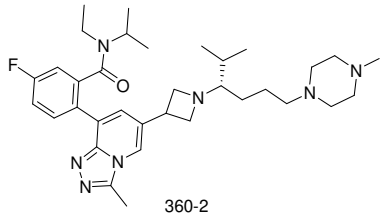

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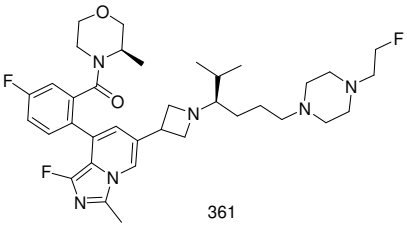

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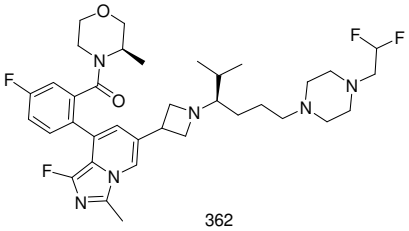

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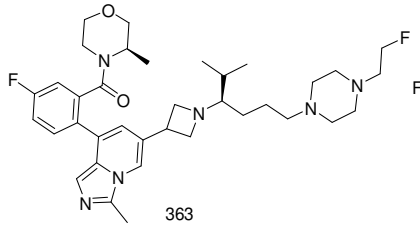

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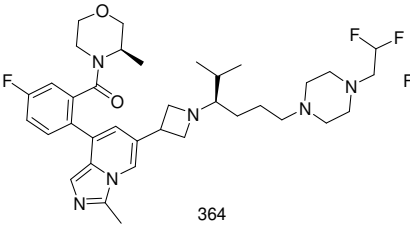

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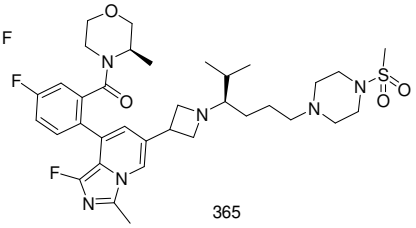

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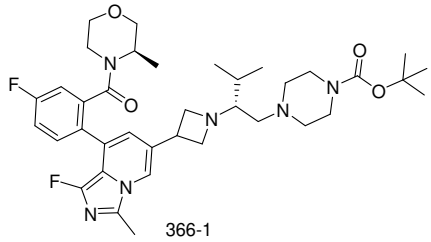
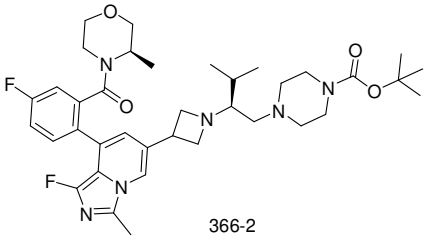


366-1



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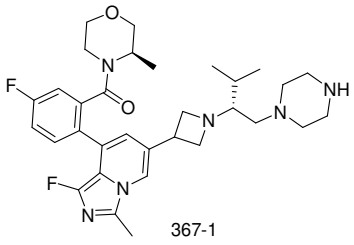

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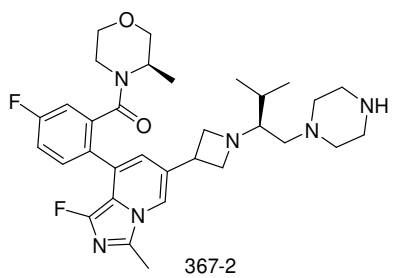

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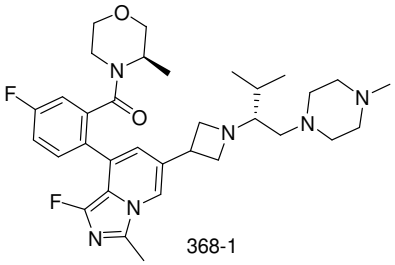

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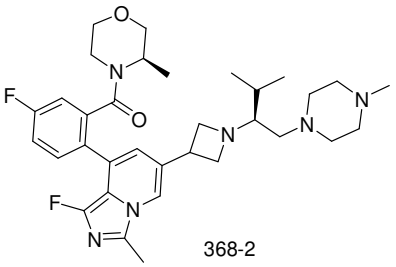

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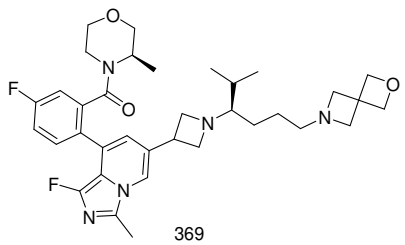

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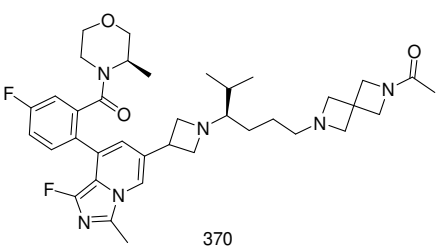

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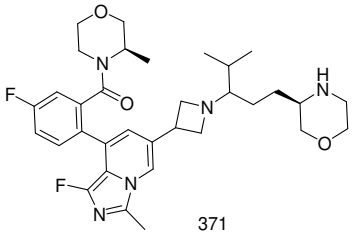

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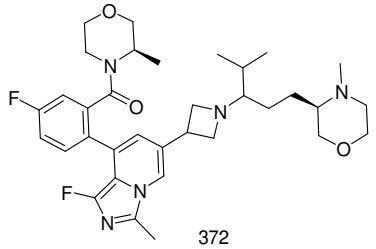

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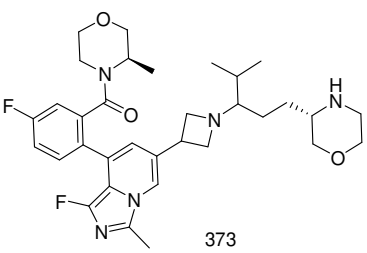

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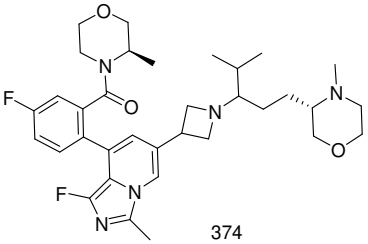

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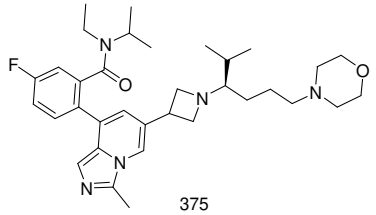

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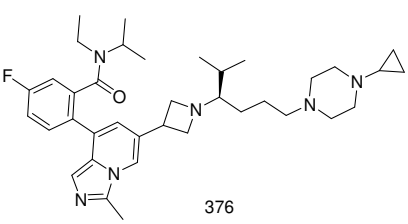

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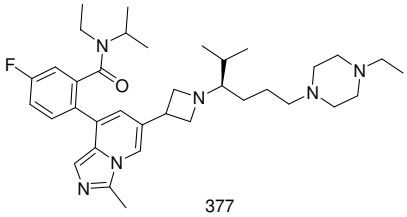

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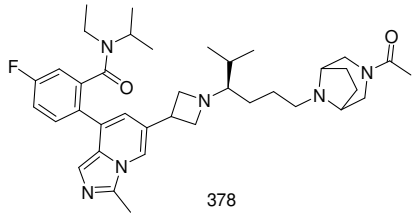

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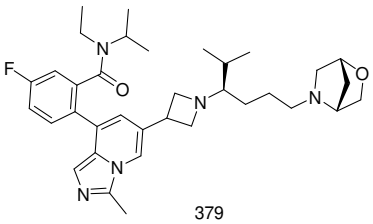

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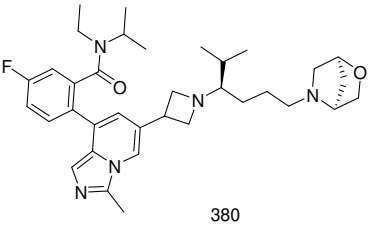

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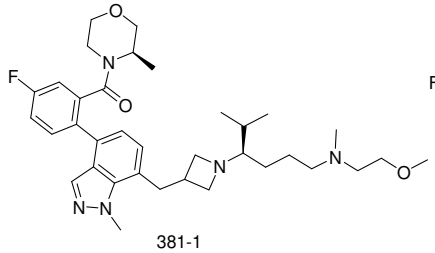

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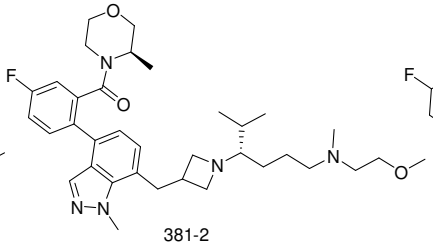

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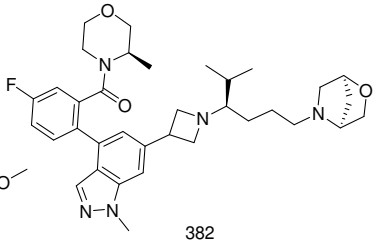

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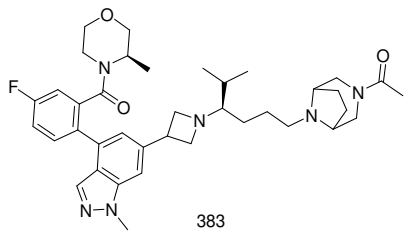

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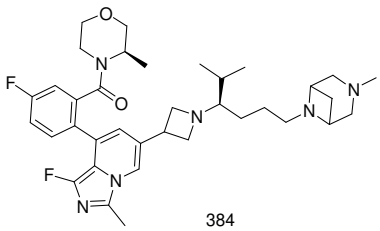

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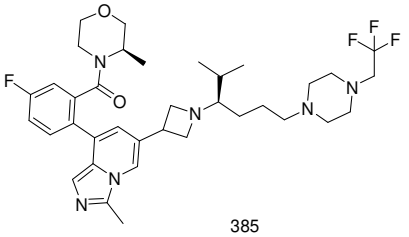

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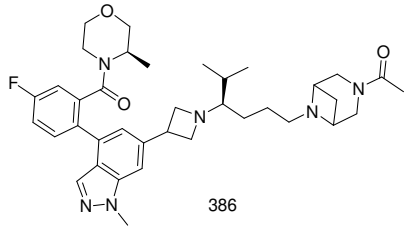

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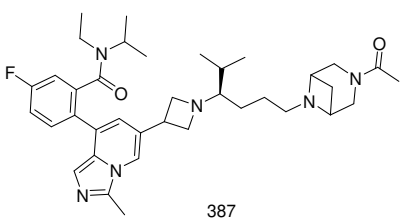

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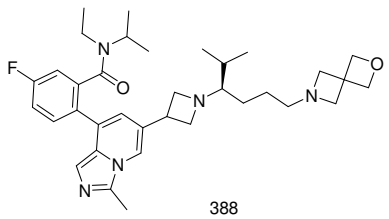

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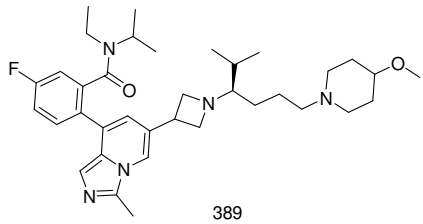

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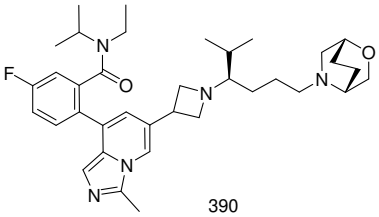

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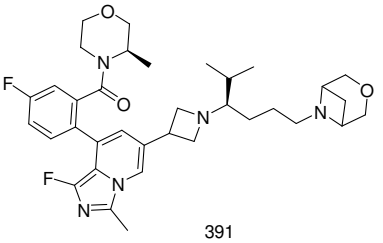

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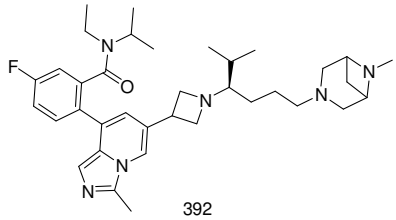

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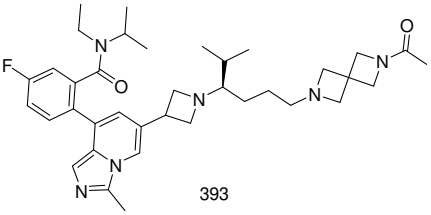

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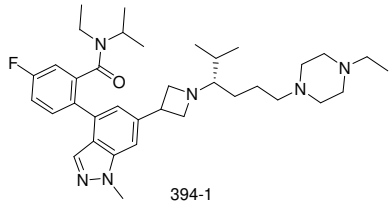
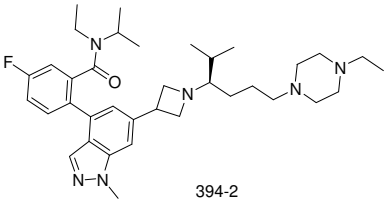
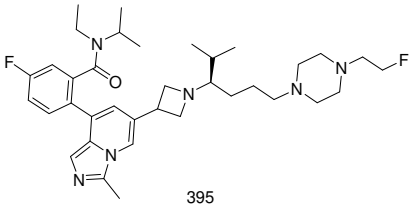


394-1



394-2



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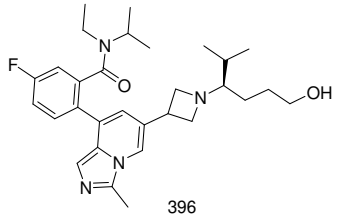

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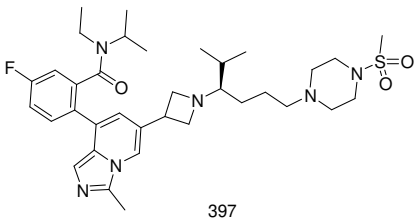

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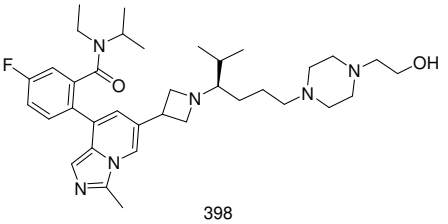

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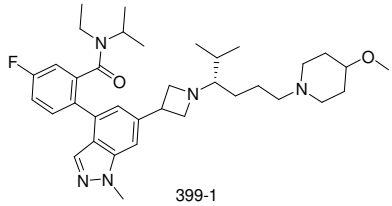

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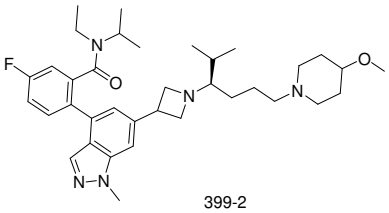
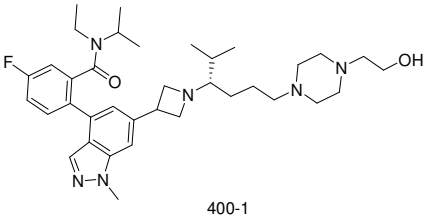
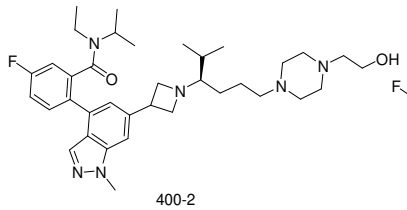


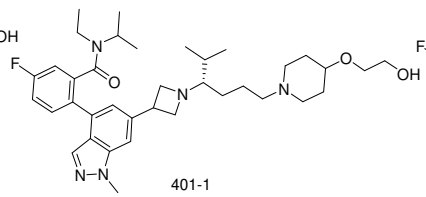
399-2



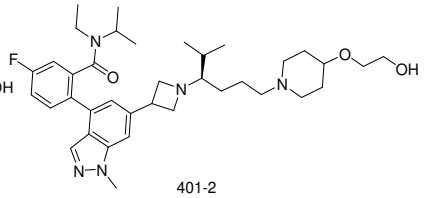
400-1



400-2



401-1



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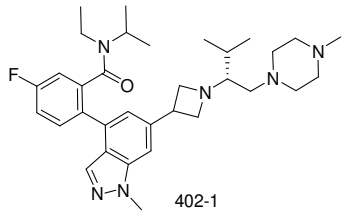

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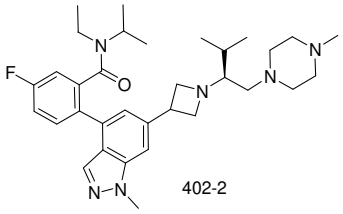

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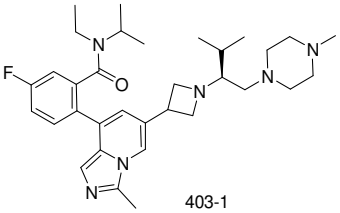

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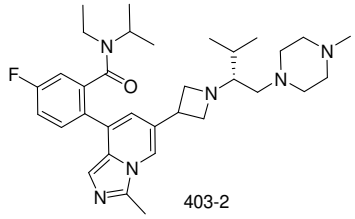

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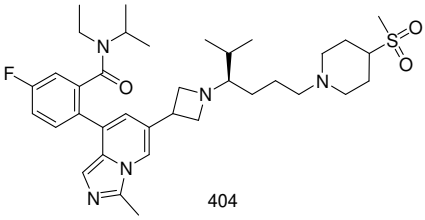

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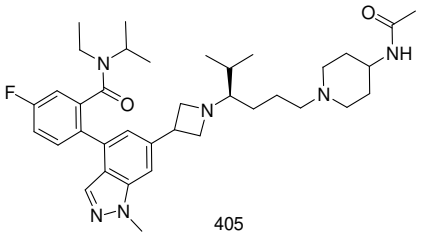

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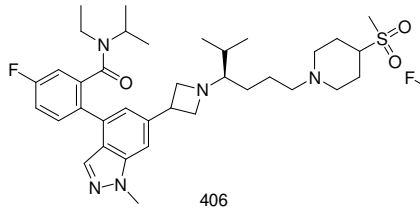

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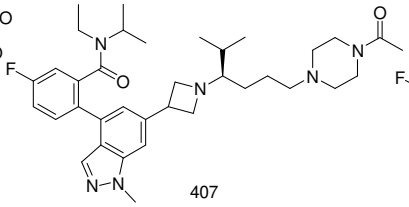

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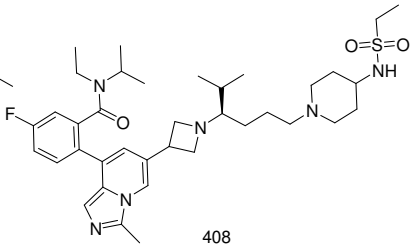

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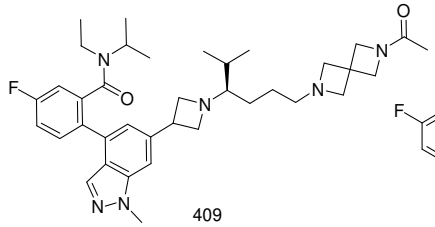

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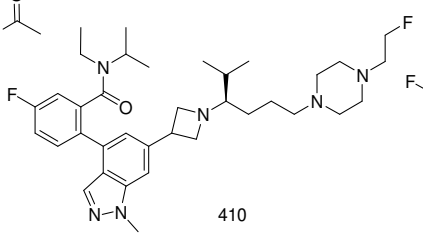

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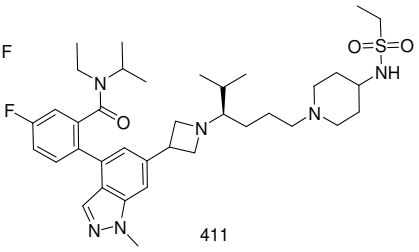

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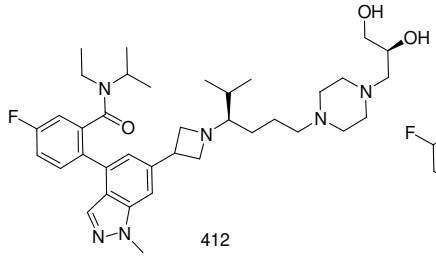

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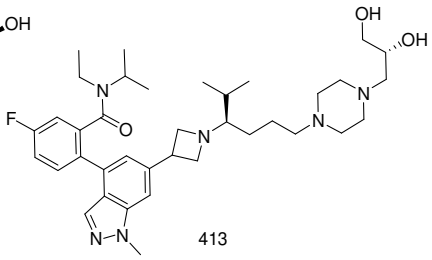

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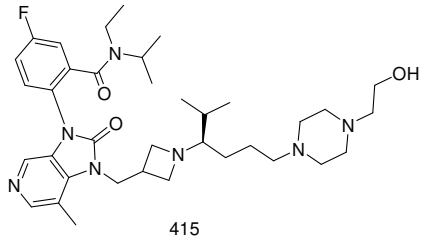

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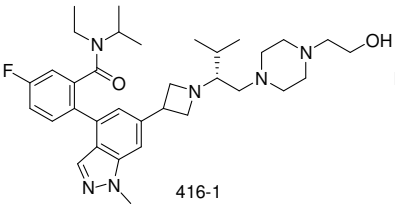

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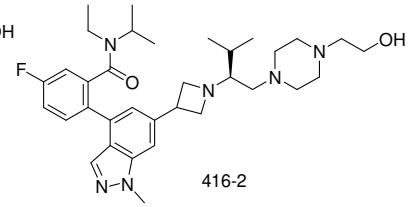

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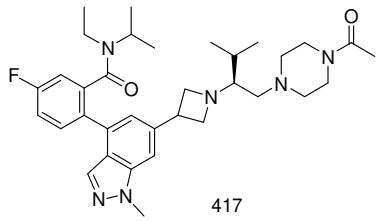

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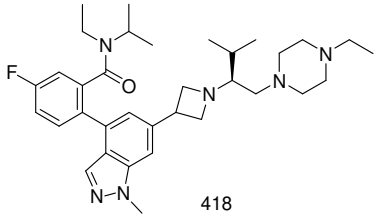

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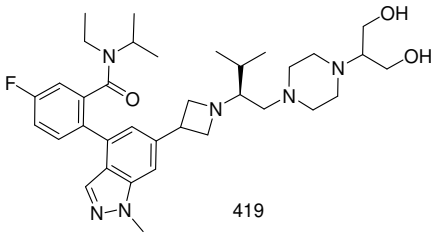

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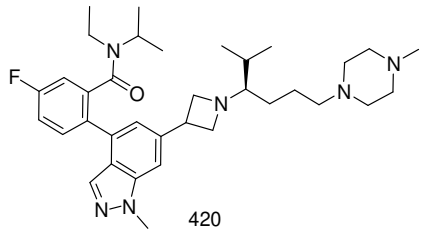

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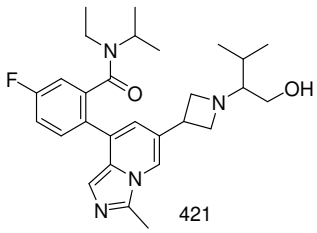

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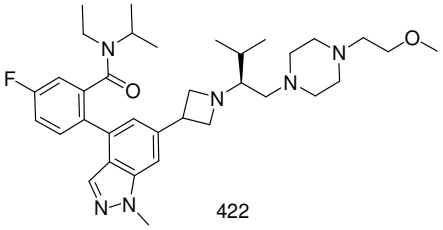

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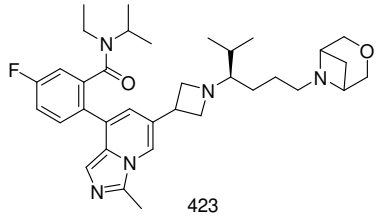

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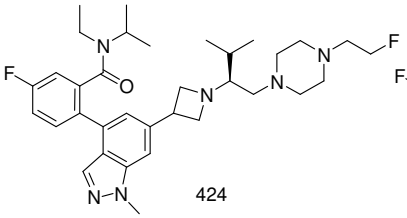

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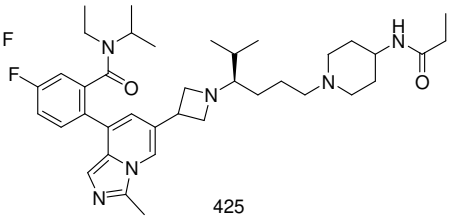

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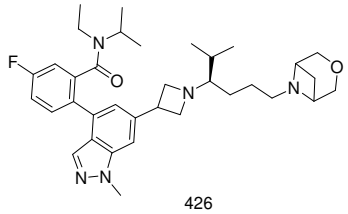

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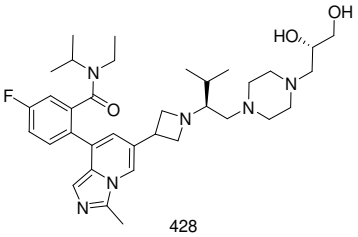

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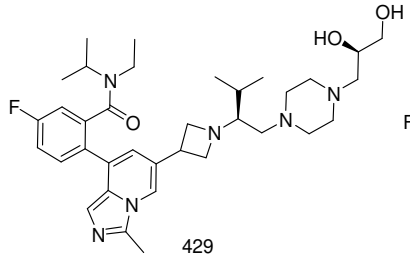

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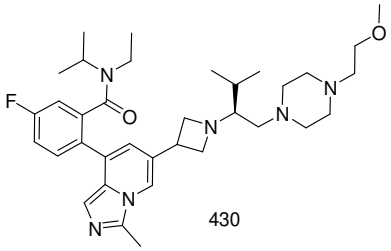

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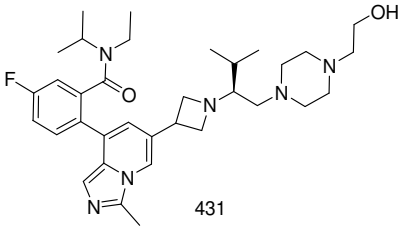

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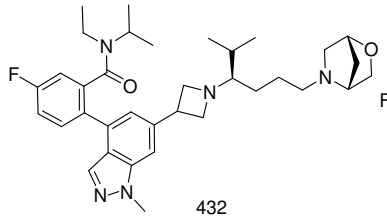

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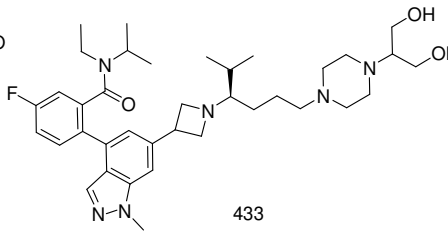

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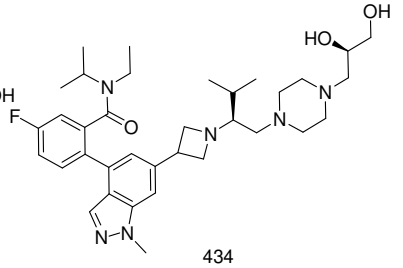

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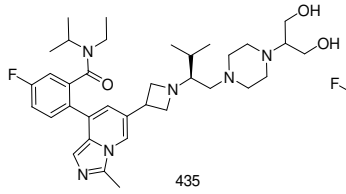

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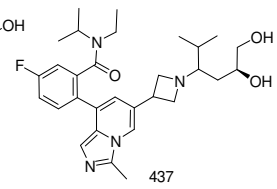

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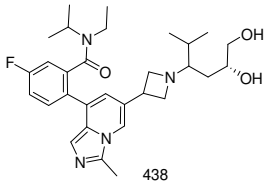

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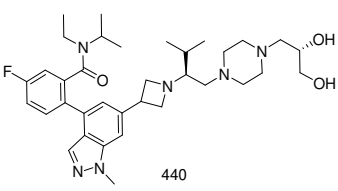

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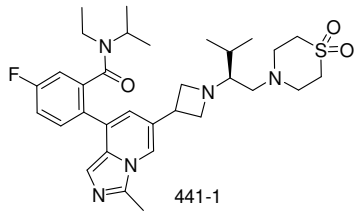

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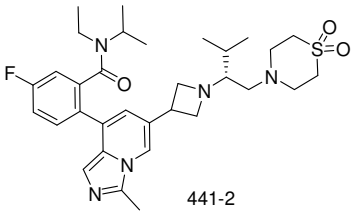

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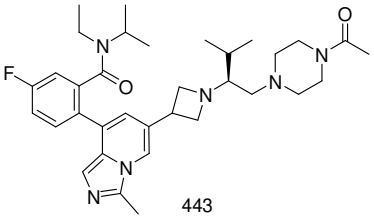

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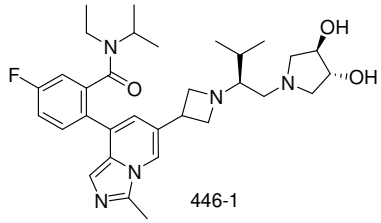

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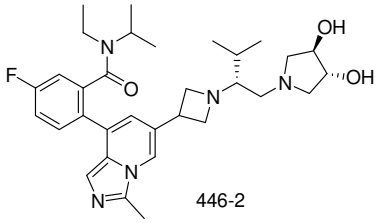

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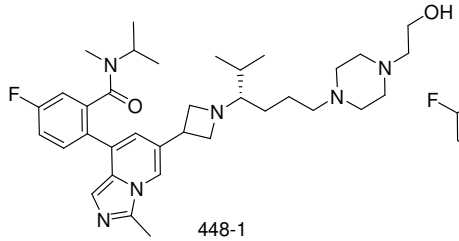

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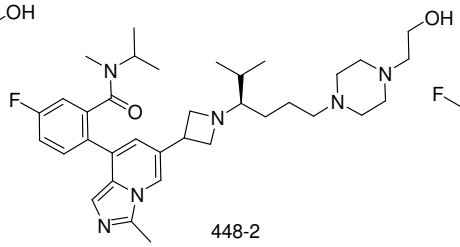

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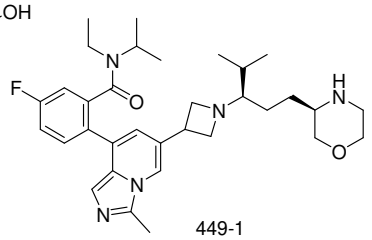

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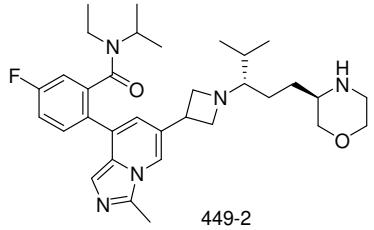

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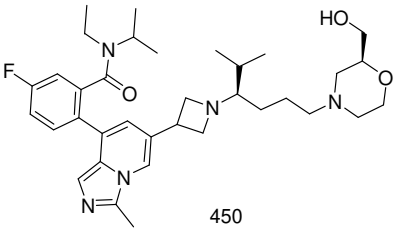

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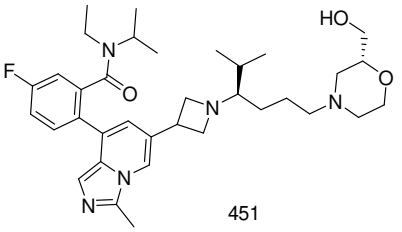

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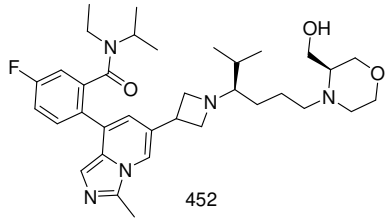

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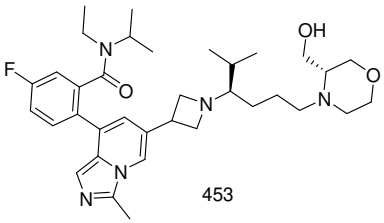

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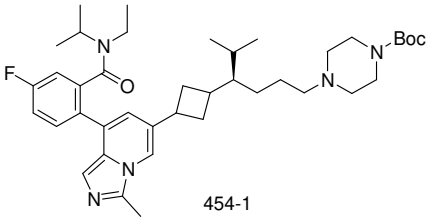

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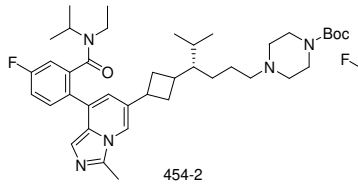

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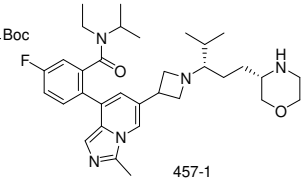

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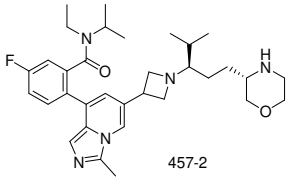

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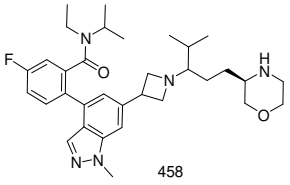

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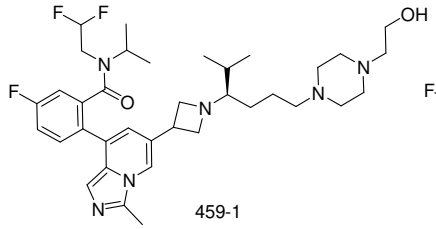

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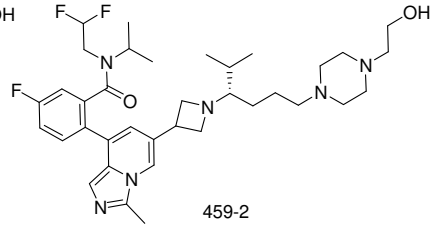

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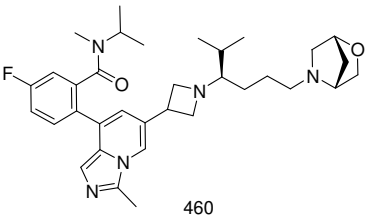

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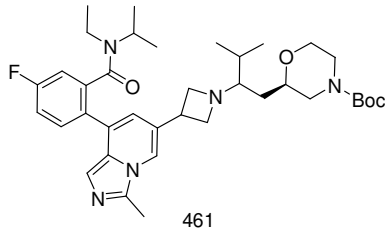

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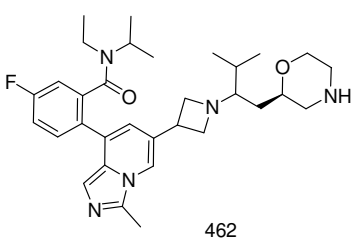

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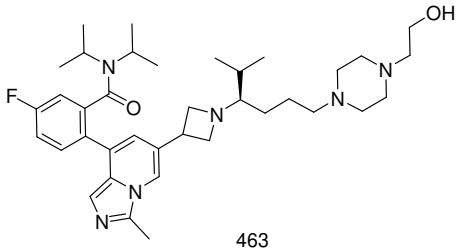

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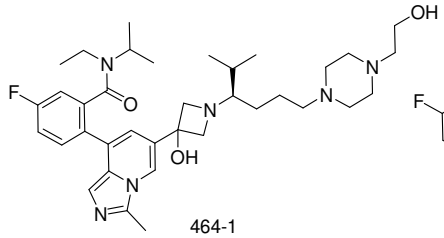

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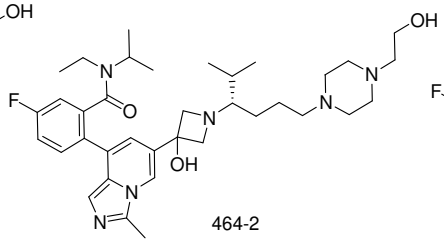

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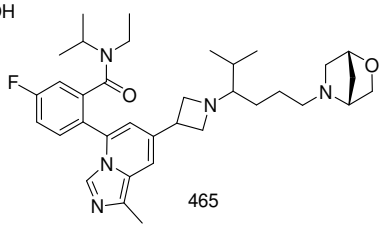

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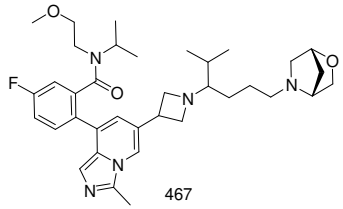

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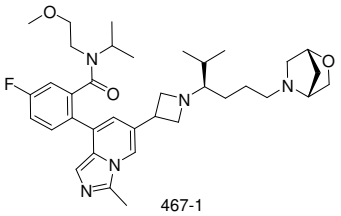

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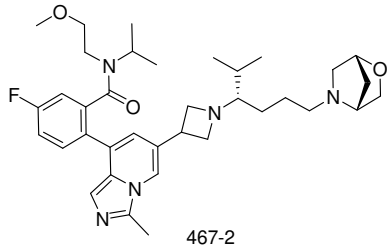

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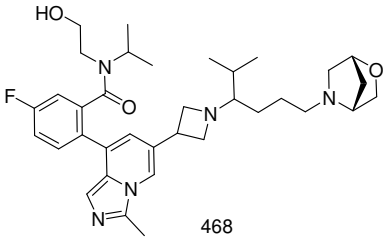

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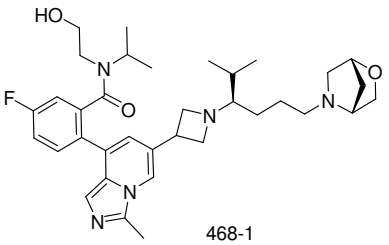

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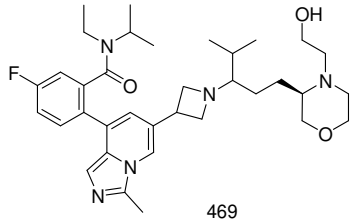

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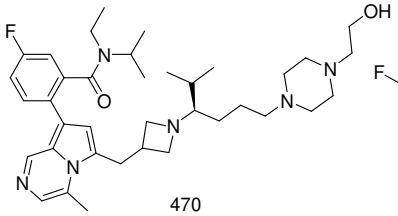

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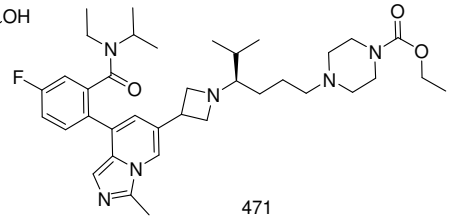

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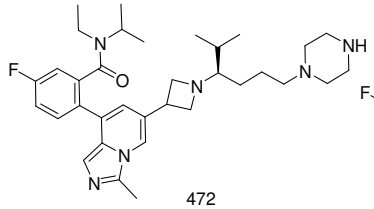

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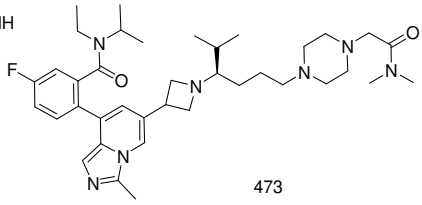

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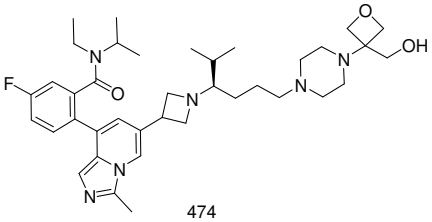

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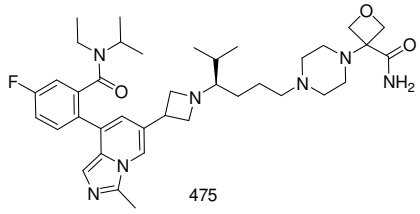

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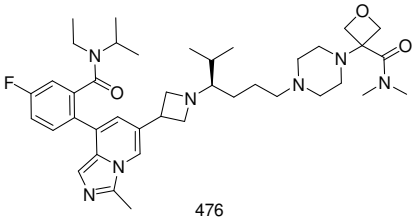

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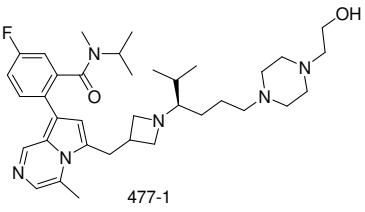

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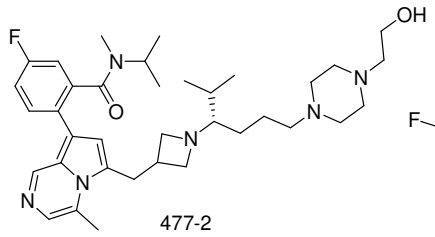

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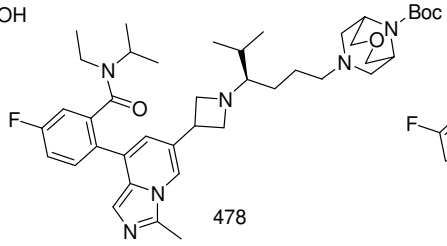

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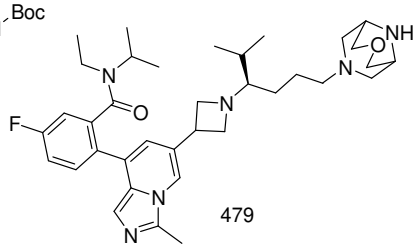

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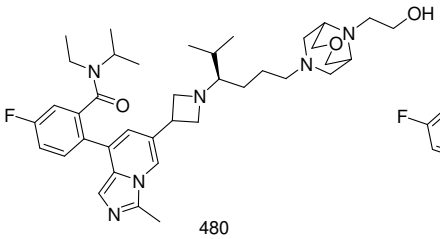

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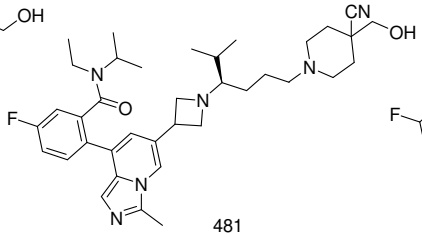

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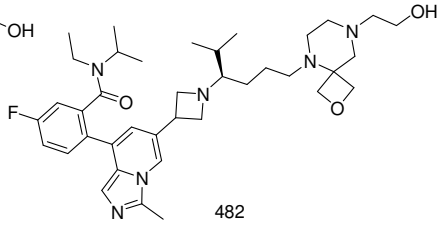

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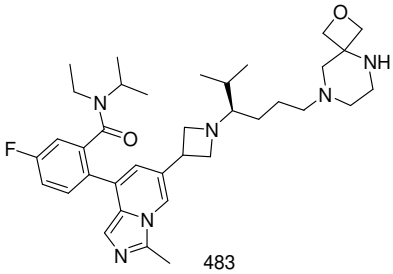

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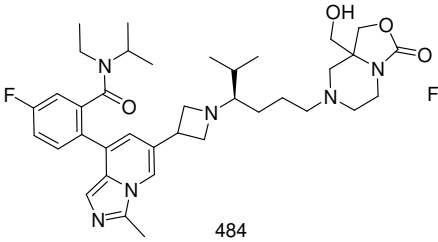

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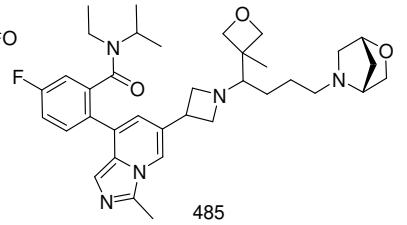

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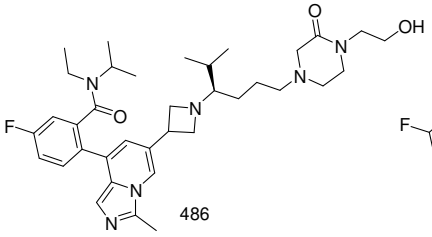

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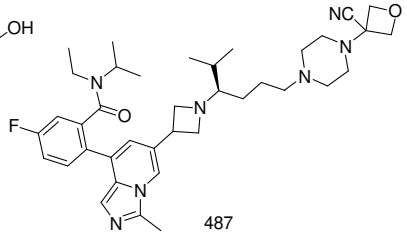

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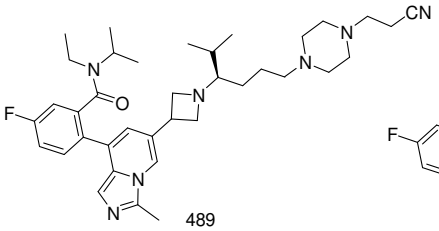

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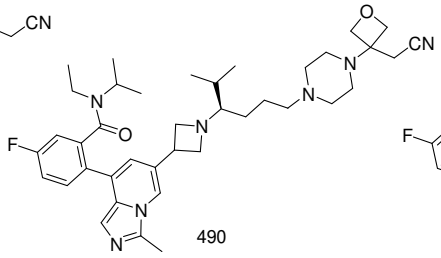

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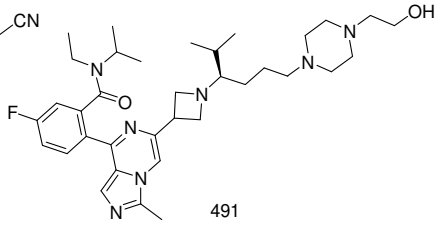

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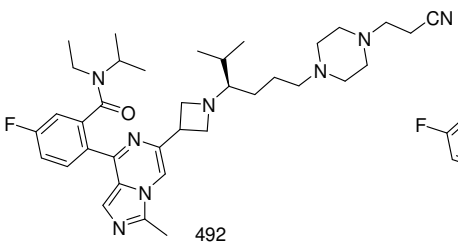

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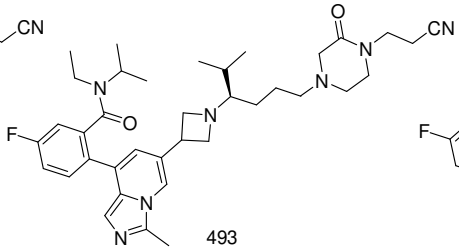

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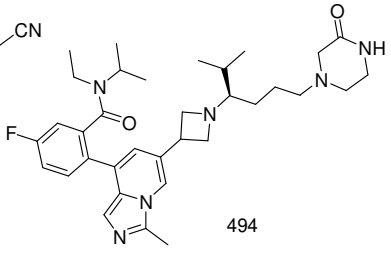

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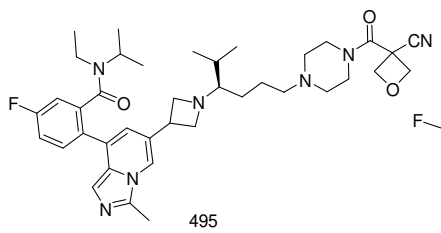

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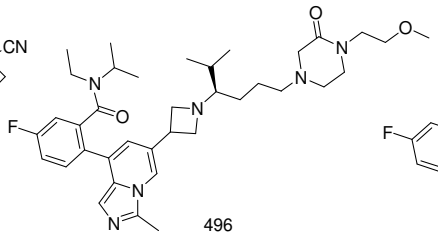

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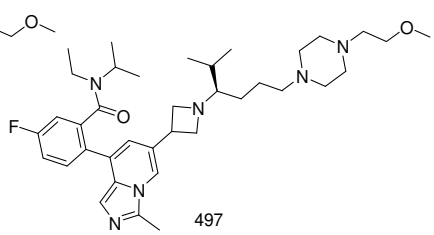

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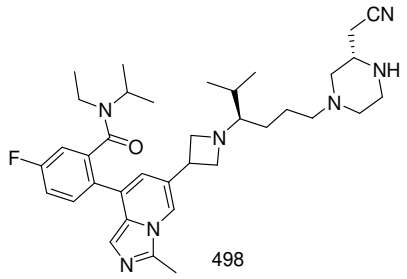

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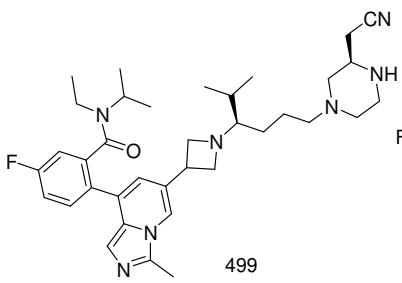

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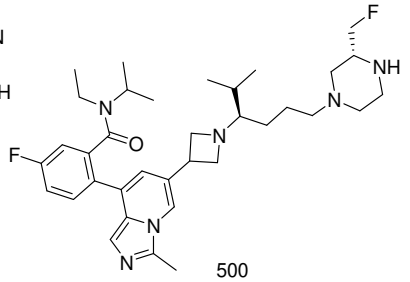

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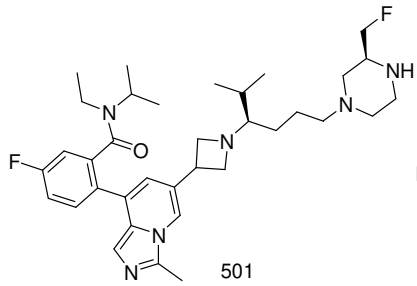

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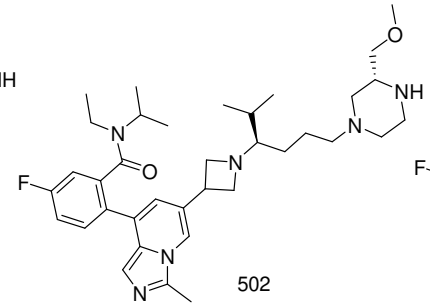

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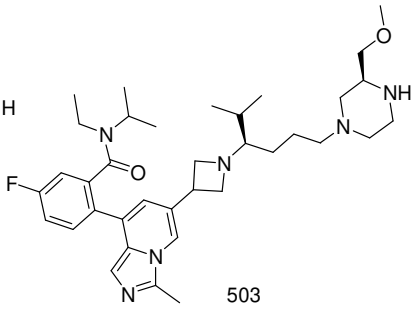

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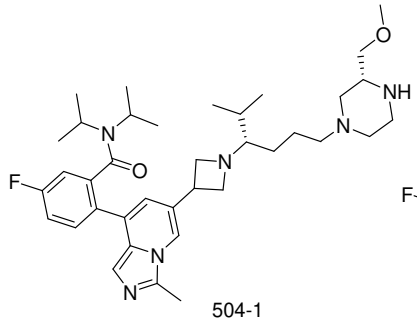

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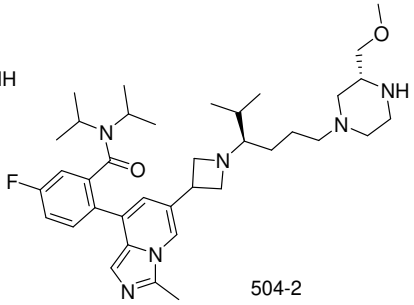

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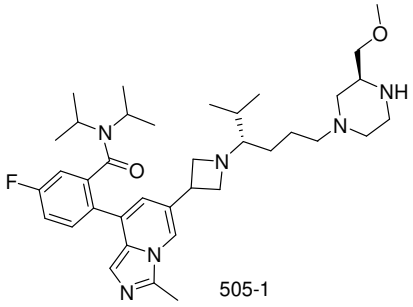

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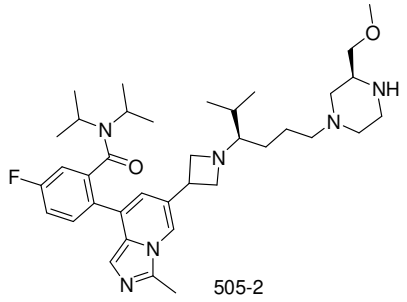

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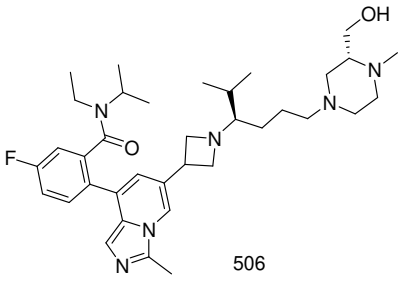

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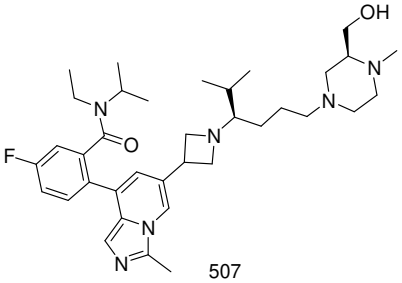

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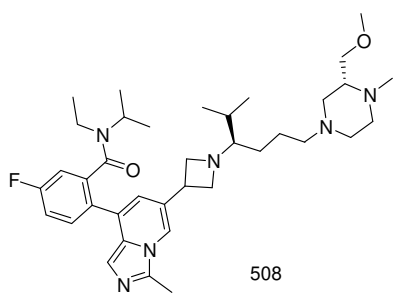
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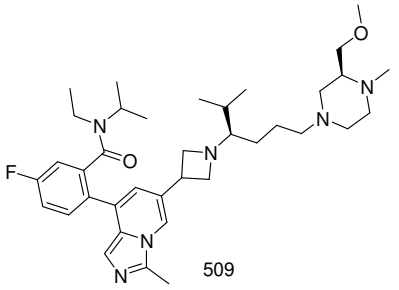
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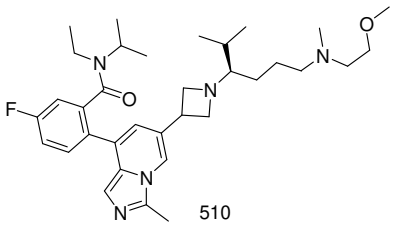
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In a second aspect of the present invention, there is provided a pharmaceutical composition, including the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, and a pharmaceutically acceptable excipient.

Specifically, the pharmaceutically acceptable excipient may be selected from one or more of: disintegrants, binders, lubricants, suspending agents, stabilizers, fillers, absorption promoters, surfactants, flavoring agents, antioxidants, preservatives, etc.

Specifically, in this pharmaceutical composition, the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate, and deuterated compound thereof, may be used alone, or in combination with other types of active ingredients.

Specifically, the pharmaceutical composition may be delivered via any appropriate route of administration, for example, gastrointestinal administration routes (for example, oral, sublingual, or rectal administration) or non-gastrointestinal administration (for example, intravenous, intramuscular, intranasal, intraocular, intracranial, vaginal, intraperitoneal, transdermal, subcutaneous, intradermal, or respiratory administration) routes.

Specifically, the pharmaceutical composition may take any suitable dosage form, for example: gastrointestinal dosage forms, for example, including but not limited to, tablets, pills, powders, granules, capsules, troches, syrups, liquids, emulsions, suspensions, etc.; and non-gastrointestinal dosage forms, such as injectable dosage forms (for example, for subcutaneous, intravenous, intramuscular, or intraperitoneal injection), respiratory dosage forms (for example, sprays, aerosols, or powder aerosols), dermal dosage forms (for example, topical solutions, lotions, ointments, plasters, pastes, or patches), mucosal dosage forms (for example, eye drops, ophthalmic ointments, nasal drops, gargles, or sublingual tablets), and cavity dosage forms (for example, suppositories, aerosols, effervescent tablets, drops, or pills) for the rectum, vagina, urethra, nose, ear canal, etc.

Specifically, various dosage forms of the aforementioned pharmaceutical composition may be prepared according to conventional production methods in the field of pharmacy. For example, an active ingredient is mixed with one or more pharmaceutically acceptable excipients to prepare the pharmaceutical composition of a desired dosage form.

Specifically, in the aforementioned pharmaceutical composition, the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof may have a weight percentage of 0.1-99.5%, for example, 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99%, in particular 1-30%.

In a third aspect of the present invention, there is provided use of the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof in the preparation of a medicament for inhibiting Menin-MLL interaction.

In a fourth aspect of the present invention, there is provided use of the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof in the preparation of a medicament for preventing and/or treating a disease mediated by Menin-MLL interaction.

In some embodiments of the present invention, the disease is a tumor, including, but not limited to, a hematological tumor (for example, leukemia or lymphoma), bladder cancer, brain cancer (for example, glioma or diffuse intrinsic pontine glioma (DIPG)), breast cancer (for example, triple-negative breast cancer or estrogen receptor-positive breast cancer (i.e., ER + breast cancer)), intestinal cancer (for example, colon cancer, rectal cancer or colorectal cancer), gastrointestinal stromal tumor (GIST), cervical cancer, gastric cancer, genitourinary cancer, head and neck cancer, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer (for example, castration-resistant prostate cancer), kidney cancer (for example, renal cell carcinoma), skin cancer, thyroid cancer (for example, papillary thyroid cancer), testicular cancer, glioblastoma, sarcoma (for example, Ewing's sarcoma), and AIDS-related cancers.

In some embodiments of the present invention, the tumor is a hematological tumor, for example, leukemia,

lymphoma, myeloma, etc.
In some embodiments of the present invention, the tumor is a solid tumor, for example, prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma, or glioblastoma.
In some embodiments of the present invention, the disease includes, but is not limited to, mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with MLL rearrangement or MLL gene rearrangement, acute leukemia, chronic leukemia, lymphoblastic leukemia, lymphocytic leukemia, myelocytic leukemia, myeloid leukemia, childhood leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute myelogenous leukemia, acute non-lymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), treatment-related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disorder (MPD) , myeloproliferative neoplasia (MPN), plasmacytoma, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid tumors, hairy cell leukemia, leukemic meningitis, multiple myeloma, Hodgkin lymphoma, and non-Hodgkin lymphoma (malignant lymphoma).
In some embodiments of the present invention, the disease is diabetes, insulin resistance, or hyperglycemia.
In some embodiments of the present invention, the diseases is an autoimmune disease.
In some embodiments of the present invention, the disease is non-alcoholic hepatitis.
In a fifth aspect of the present invention, there is provided a method for inhibiting Menin-MLL interaction, including: administering the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, or the pharmaceutical composition described in the second aspect.
In some embodiments of the present invention, the method is performed in vitro.
In some embodiments of the present invention, the method is performed in vivo.
In a sixth aspect of the present invention, there is provided a method for preventing and/or treating a disease mediated by Menin-MLL interaction, including: administering the compound described in the first aspect or the pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, or the pharmaceutical composition described in the second aspect, to a subject in need thereof.
Specifically, the disease is defined as in the fourth aspect of the present invention.
Specifically, the subject is a mammal, in particular a human.

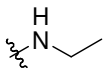
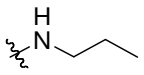
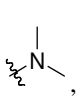
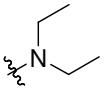
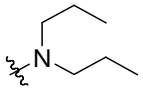
DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all scientific and technical terms used in the present invention have the same meanings as those generally understood by those of ordinary skill in the art that is involved in the present invention.
In the present invention, the term “aliphatic group” refers to a linear or branched hydrocarbon chain that is completely saturated or contains one or more unsaturated units, or a cyclic hydrocarbon group (also referred to herein as “carboatomic ring” or “aliphatic ring”) that is completely saturated or contains one or more unsaturated units, and the aliphatic group is attached to the remainder of the molecule via a single bond. Suitable aliphatic groups include, but are not limited to, linear or branched and substituted or unsubstituted alkyl, alkenyl, alkynyl, and their mixtures, for example, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (cycloalkyl)alkenyl, etc. A typical aliphatic group contains 1 to 10 (for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) carbon atoms, preferably 1 to 6 carbon atoms.
The term “alkyl” refers to a linear or branched hydrocarbon chain free radical that contains no unsaturated bond, and the hydrocarbon chain free radical is attached to the remainder of the molecule via a single bond. A typical alkyl group contains 1 to 10 (for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) carbon atoms, preferably 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-amyl, isoamyl, neoamyl, tert-amyl, n-hexyl, isohexyl, etc. If alkyl is substituted with cycloalkyl, then “cycloalkylalkyl” is derived correspondingly, for example, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, etc. Typical cycloalkylalkyl groups include C_3-C_{10} cycloalkylalkyl, for example, -(C_1-C_3 alkylene)-(C_3-C_6 cycloalkyl). If alkyl is substituted with aryl, then “aralkyl” is derived correspondingly, for example, benzyl, diphenylmethyl, or phenylethyl. If alkyl is substituted with heterocyclyl, then “heterocyclylalkyl” is derived correspondingly. In the present invention, C_0 alkyl refers to H, that is, C_{0-10} alkyl includes H and C_{1-10} alkyl.
The term “alkylene” refers to a hydrocarbon group (divalent alkyl group) derived by removing two hydrogen atoms from an alkane molecule, and it may be either linear or branched and is attached to the remainder of the molecule via a single bond. A typical alkylene group herein contains 1 to 10 (for example, 1, 2, 3, 4, 5, 6,

7, 8, 9, or 10) carbon atoms, preferably 1 to 6 carbon atoms, such as methylene (-CH_2-), ethylene, propylene, butylene, etc. In the present invention, C_0 alkylene refers to a single bond, that is, C_{0-10} alkylene includes a single bond and C_{1-10} alkylene.

The term "cycloalky" refers to an aliphatic cyclic hydrocarbon, including for example 1 to 4 monocyclic and/or fused rings containing 3-18 carbon atoms, preferably 3-10 (for example, 3, 4, 5, 6, 7, 8, 9, or 10) carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or adamantyl.

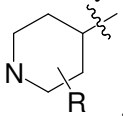
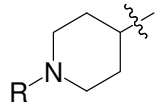
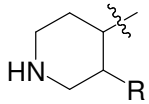
The term "alkoxy" refers to a substituent group derived from a hydroxyl group by substituting hydrogen with an alkyl group, for example, an alkoxy group containing 1-10 carbon atoms, such as methoxy, ethoxy, propoxy, butoxy, etc.

The term "alkylamino" refers to a substituent group derived from an amino group (-NH2) by substituting one or two hydrogens with an alkyl group(s), for example, an alkylamino group containing 1-10 carbon atoms, such as ,  ,  ,  ,  , and  .

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "halogenated alkyl" refers to a group derived from an alkyl group by substituting one or more hydrogens with a halogen atom(s) (for example, fluorine, chlorine, bromine, or iodine), for example,-CHF_2, -CH_2F, -CF_3, -CH_2-CH_2F, -CH_2-CHF_2, -CH_2-CF_3, -CH_2CH_2-CF_3, or -$CH_2CH_2CH_2$-CF_3.

The term "aryl" refers to a monocyclic or polycyclic free radical, including a polycyclic free radical containing a single aryl group and/or a fused aryl group, for example, containing 1-3 monocyclic or fused rings and 6-18 (for example, 6, 8, 10, 12, 14, 16, or 18) carboatomic ring atoms. In the present invention, the C_6-C_{12} aryl refers to an aryl group containing 6-12 carboatomic ring atoms, for example, phenyl, naphthyl, biphenyl, indenyl, etc.

The term "heterocyclyl" refers to a 3-18-membered cyclyl group containing 2 to 17 carbon atoms and 1 to 10 heteroatoms selected from N, O, or S atoms. The heterocyclyl group may be a monocyclic, bicyclic, tricyclic, or tetracyclic system, or an additional polycyclic system, which may include a fused (two rings sharing two ring atoms), spiro (two rings sharing one ring atom), or bridged (two rings sharing more than three ring atoms) ring system (excluding linked rings). The heterocyclyl group may be partially saturated (e.g., heteroaryl) or fully saturated (e.g., heterocycloalkyl). In the compound of the present invention, an appropriate heteroaryl group contains 1, 2 or 3 types of heteroatoms selected from N, O or S atoms, and includes, for example, coumarin (including 8-coumarin), quinolyl (including 8-quinolyl), isoquinolyl, pyridinyl, pyrazinyl, pyrazolyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, thienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridinyl. In the compound of the present invention, an appropriate heterocycloalkyl group contains 1, 2 or 3 types of heteroatoms selected from N, O or S atoms, and includes, for example, pyrrolidinyl, tetrahydrofuranyl, dihydrofuran, tetrahydrothienyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, oxathiacyclohexanyl, piperazinyl, azacyclobutanyl, oxacyclobutanyl, thiacyclobutanyl, homopiperidinyl, oxacyclopropanyl, thiacyclopropanyl, azepinyl, oxazacycloheptyl, diazepinyl, triazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, dihydroindolyl, 2H-pyranyl, 4H-pyranyl, dioxacyclohexanyl, 1,3-dioxolanyl, pyrazolinyl, dithanyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl,3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinazinyl. In the present invention, for the optionally substituted heterocyclyl group, any suitable carbon atom or heteroatom may be at the substitution position. As an example, for  , the position of substitution for R may be occupied by any suitable carbon atom or nitrogen atom, which may be, for example,  or  .

The term "optionally substituted" group may be halogen, -CN, -NO_2, -OR', -NR'R", -S(O)t-R', -S(O)t-NR'R", -COR', -C(O)OR', -C(O)NR'R", -C(O)N(R')OR", -OC(O)R', -OC(O)NR'R", -NR'C(O)R", -N(R')C(O)NR'R', -N(R')C(NR')NR'R', -NR'-S(O)t-R', -NR'-S(O)t-NR'R', -N=S(O)R'R", -S(NR')(O)R", -N(R')CN, -P(O)(R')NR'R", -P(O)(R')OR" or -P(O)R'R", C_{1-6} alkyl, C_{1-6} halogenated alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{3-6} cycloalkyl, C_{4-10} cycloalkylalkyl, C_{6-10} aryl, C_{6-10} arylalkyl, C_{3-8} heterocyclyl, or C_{3-8} heterocyclylalkyl; t is 0, 1 or 2; R' and R" are each independently selected from the group consisting of: H, halogen, -CN, -NO_2, alkyl, halogenated alkyl,

cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; or, R' and R'', which are linked to the same nitrogen, form a heterocyclic ring together with this nitrogen atom.

The term "pharmaceutically acceptable salt" includes acid addition salts and alkali addition salts.

The term "acid addition salts" includes, but is not limited to, salts derived from inorganic acids (such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, and phosphonic acid), as well as salts derived from organic acids (such as aliphatic monocarboxylic and dicarboxylic acids, phenyl-substituted alkanoic acid, hydroxyalkanoic acid, dialkanoic acid, aromatic acid, and aliphatic and aromatic sulfonic acid). The acid addition salts include, for example, acetate, salicylate, decanoate, stearate, oleate, caproate, malate, glycolate, ethanesulfonate, hydroxyesulfonate, etc. Therefore, these salts include, but are not limited to, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, hydrochloride, hydrobromide, iodate, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, amygdalate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, tosylate, phenylacetate, citrate, lactate, tartrate and methanesulfonate, and further include salts of amino acids, such as arginine, gluconate, galacturonate, aspartate, glutamate, etc. The acid addition salts may be prepared by bringing free alkali into contact with a sufficient amount of the desired acid in a conventional way. The free alkali may be regenerated by bringing a salt into contact with an alkali, and may be isolated in a conventional way.

The term "alkali addition salts" refer to salts formed with metals or amines (such as hydroxides of alkali metals and alkaline earth metals), or with organic amines. Examples of metals used as cations include, but are not limited to, sodium, potassium, magnesium, and calcium. Examples of suitable amines include, but are not limited to, N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine(ethane-1,2-diamine), N-methylglucosamine, and procaine. The alkali addition salts may be prepared by bringing free acid into contact with a sufficient amount of the desired alkali in a conventional way. The free acid may be regenerated by bringing a salt into contact with an acid, and may be isolated in a conventional way.

The term "stereoisomer" exists as enantiomers, diastereomers, and geometric isomers. Some compounds of the present invention have a cyclic hydrocarbon group, which may be substituted on more than one carbon atom, in which case all their geometric forms (including cis and trans forms), and their mixtures, shall fall within the scope of the present invention.

The term "solvate" refers to the physical binding of the compound of the present invention to one or more solvent molecules. This physical binding includes ionic and covalent bonding to various degrees, including hydrogen bonding. In some cases, the solvate may be isolated, for example, where one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. The solvate includes solution phases and separable solvates. Representative solvates include alcoholate, methylate, etc.

The term "deuterated compound" refers to a compound in which one or more hydrogen atoms (for example, 1, 2, 3, 4, or 5 hydrogen atoms) are substituted with deuterium atoms (D).

It should be recognized that, depending on the source of the chemical material used for synthesis, the abundance of natural isotopes varies in the synthesized compounds. Therefore, the compound of the present invention will inherently comprise a small amount of deuterated isotopologues. Despite this variation, the concentrations of stable hydrogen and carbon isotopes of this natural abundance are still low and insignificant compared to the degree of stable isotope substitution in the compound of the present invention. A reference can be made to, for example, Wada, E et al., Seikagaku, 1994, 66: 15; and Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119: 725. In the compound of the present invention, any atom that is not specified as deuterium exists in its natural isotope abundance. Unless otherwise indicated, when a position is specifically specified as "H" or "hydrogen", this position shall be understood as having hydrogen with the isotopic composition corresponding to its natural abundance. Similarly, unless otherwise indicated, when a position is specifically specified as "D" or "deuterium", this position shall be understood as having deuterium with the abundance of at least 3000 times greater than the natural abundance (which is 0.015%) of deuterium (i.e., at least 45% of deuterium incorporated).

The term "isotope enrichment coefficient" as used herein refers to the ratio of the isotopic abundance of a particular isotope to its natural abundance.

In other embodiments, the isotope enrichment coefficient of the compound of the present invention for each specified deuterium atom is at least 3500 (with 52.5% of deuterium incorporated at each specified deuterium atom), at least 4000 (with 60% of deuterium incorporated), at least 4500 (with 67.5% of deuterium incorporated), at least 5000 (with 75% of deuterium incorporated), at least 5500 (with 82.5% of deuterium incorporated), at least 6000 (90% of deuterium incorporated), at least 6333.3 (with 95% of deuterium incorporated), at least 6466.7 (with 97% of deuterium incorporated), at least 6600 (with 99% of deuterium incorporated) or at least 6633.3 (with 99.5% of deuterium incorporated).

The term "isotopologue" refers to a substance with a chemical structure differing from the specific compound of the

present invention only in its isotopic composition.
The term “prodrug” refers to the compound forms of formula I (including acetal, ester and zwitterionic forms), which are suitable for administration to patients without excessive toxicity, irritation, allergic reactions or the like and are effective for the purpose of their application. The prodrug is transformed in vivo, for example, by hydrolysis in the blood, to obtain a parent compound.
The terms “patient” or “subject” and the like are used interchangeably herein, referring to any animals or their cells that have been treated according to the methods described herein, whether in vitro or in situ. Specifically, the aforementioned animals include mammals, for example, rats, mice, guinea pigs, rabbits, dogs, monkeys, and humans, in particular humans.
The term “treatment” refers to the process of preventing, curing, reversing, attenuating, alleviating, minimizing, inhibiting, restraining and/or stopping one or more clinical symptoms of a disease after its onset.
The term “prevention” refers to the process of treating a disease, before its onset, in order to avoid, minimize, or make it difficult for the disease to occur or progress.
The term "tumor" refers to a neoplasm formed by the proliferation of local tissue cells in the body under the action of various tumorigenic factors. Based on the cell characteristics of the neoplasm and its degree of harm to the body, tumors are further divided into two major categories: benign tumors and malignant tumors. "Malignant tumors" refer to diseases that are characterized by uncontrollable growth and spread of malignant cells, along with tissue infiltration, and are determined through pathological examination to meet the criteria for classification as malignant tumors according to the "Classification of Diseases and Causes of Death" standards published by the Ministry of Health.
In specific embodiments, the compound of the present invention is for use in the treatment of leukemia associated with MLL rearrangement, acute lymphogenous leukemia associated with MLL rearrangement, acute lymphoblastic leukemia associated with MLL rearrangement, acute lymphoid leukemia associated with MLL rearrangement, acute myeloid leukemia associated with MLL rearrangement, acute myelogenous leukemia associated with MLL rearrangement, or acute myeloblastic leukemia associated with MLL rearrangement. As used in the present application, "MLL rearrangement" means the rearrangement of MLL genes.
The term "autoimmune disease" refers to a disease caused by the body's immune response to its own antigens, resulting in damage to its own tissues. It can be divided into organ-specific autoimmune diseases (mainly affecting a single organ) and systemic autoimmune diseases (affecting multiple tissues or organs throughout the body). The American Autoimmune Related Diseases Association has listed a relatively comprehensive list of autoimmune diseases, among which common autoimmune diseases typically include: systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, psoriasis, celiac disease, ulcerative colitis, Crohn's disease, etc.
Unless otherwise indicated, the range of values expressed in the form “from x to y” or “x-y” shall be understood as including x and y. When several preferred ranges are described in the form of “from x to y” or “x-y” for a specific feature, it should be understood that all ranges combining different endpoints can also be considered.
The disclosures of all the publications, patents and published patent specifications cited herein are incorporated herein by reference in their entireties.
The technical solutions of the present invention will be described clearly and completely below in conjunction with the embodiments of the present invention. Obviously, the embodiments described are only part of rather than all of the embodiments of the present invention. Based on the embodiments in the present invention, all other embodiments obtained by those ordinarily skilled in the art without making inventive efforts shall fall within the protection scope of the present invention.

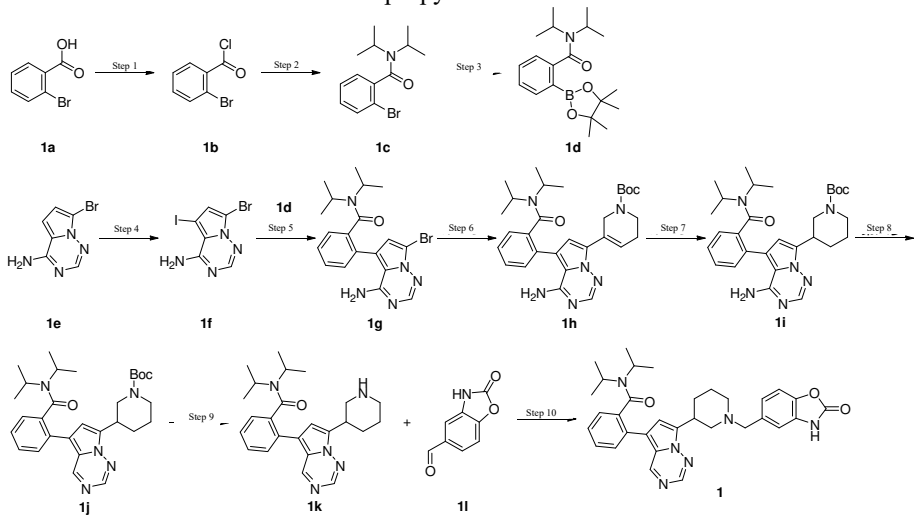
Synthesis Examples

The structure of the compound was determined by nuclear magnetic resonance (NMR) or/and mass spectrometry (MS). NMR shifts (δ) were given in units of 10^{-6} (ppm). NMR measurements were performed using a Bruker AVANCE-400 NMR spectrometer or a Bruker AVANCE NEO 500M. The measurement solvents included deuterated dimethyl sulfoxide (DMSO-d_6), deuterated chloroform ($CDCl_3$) and deuterated methanol (CD_3OD), with tetramethylsilane (TMS) serving as the internal standard.
MS measurements were performed using an Agilent 1200/1290 DAD-6110/6120 Quadrupole LC-MS instrument (manufacturer: Agilent; MS model: 6110/6120 Quadrupole MS), waters ACQuity UPLC-QD/SQD (manufacturer: waters; MS model: waters ACQuity Qda Detector/waters SQ Detector), and THERMO Ultimate 3000-Q Exactive (manufacturer: THERMO; MS model: THERMO Q Exactive).
High-performance liquid chromatography (HPLC) analysis was performed using Agilent HPLC 1200DAD, Agilent HPLC 1200VWD and Waters HPLC e2695-2489 high-pressure liquid chromatographs.
Chiral HPLC analytic determination was performed using the Agilent 1260 DAD high-performance liquid

chromatograph.
High-performance liquid phase preparation was performed using Waters 2767, Waters 2767-SQ Detecor2, Shimadzu LC-20AP and Gilson-281preparative chromatographs.
Chiral preparation was performed using a Shimadzu LC-20A preparative chromatograph.
Combiflash Rf200 (TELEDYNE ISCO) was used as the CombiFlash rapid preparation chromatograph.
Yantai Huanghai HSGF254 or Qingdao GF254 silica gel plates were used for thin-layer chromatography (TLC), with the size of 0.15 mm to 0.2 mm for TLC and the size of 0.4 mm to 0.5 mm for products separated and purified by the TLC.
For silica-gel column chromatography, Yantai Huanghai Silica Gel 200-300-mesh silica gel was generally used as the carrier.
Kinase average inhibition rate and IC_{50} value were measured using NovoStar microplate reader (BMG, Germany).
The known starting materials of the present disclosure were synthesized by methods known in the art, or purchased from ABCR GmbH & Co. KG, Acros Organics, Aldrich Chemical Company, Accela ChemBio Inc, Darui Chemical and other companies.
Unless otherwise specified in the examples, the reactions can be carried out under an argon or nitrogen atmosphere.
The argon or nitrogen atmosphere refers to the condition where a reaction flask is connected to an argon or nitrogen balloon with a volume of about 1 L.
The hydrogen atmosphere refers to the condition where a reaction flask is connected to a hydrogen balloon with a volume of about 1 L.
A hydrogenator or an autoclave was used for the pressurized hydrogenation reaction.
The hydrogenation reaction typically includes evacuating, filling with hydrogen, and repeating 3 times.
A CEM Discover-S 908860 microwave reactor was used for the microwave reaction.
Unless otherwise specified in the examples, the solution refers to an aqueous solution.
Unless otherwise specified in the examples, the reaction temperature refers to room temperature, which is 20°C to 30°C.
The reaction process in the examples was monitored by TLC. The developing solvent used in the reaction, the eluent system for column chromatography used to purify the compounds, and the developing solvent system for TLC included: an n-hexane/ethyl acetate system, a dichloromethane/methanol system, a dichloromethane/ethyl acetate system, etc. The volume ratio of solvents was regulated based on the polarity of the compounds, or small amounts of basic or acidic reagents (such as triethylamine and acetic acid) could also be added for adjustment.

Example 1

2-(7-{1-[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]piperidin-3-yl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)-*N,N*-diisopropylbenzamide **1**



Step 1

2-Bromobenzoyl chloride **1b**

2-Bromobenzoic acid **1a** (5.00 g, 24.9 mmol) was dissolved in dichloromethane (35 mL), and cooled to 0°C. Under a nitrogen atmosphere, oxalyl chloride (3.79 g, 29.9 mmol) and *N,N*-dimethylformamide (0.1 mL) were added, and the mixture was stirred at room temperature for 1.0 hour. The dichloromethane solution of title Compound **1b** was then obtained, which was directly used in the next step of reaction without treatment.

Step 2

2-bromo-*N,N*-diisopropylbenzamide **1c**

The dichloromethane solution of Compound **1b** prepared from the previous step was cooled to 0°C, diisopropylamine (46.1 g, 455 mmol) was added, and the mixture was stirred at room temperature for 12 hours. 2N aqueous hydrochloric acid solution was added to regulate the PH value of the reaction mixture to 2-3, and the reaction mixture was diluted with water (10 mL), and extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate and concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the title Compound **1c** (6.32 g, 22.2 mmol, two-step yield: 89.2%).

MS m/z (ESI): 283.9 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.34 – 7.24 (m, 2H), 3.58 (dt, J = 13.6, 6.8 Hz, 1H), 3.45 (dt, J = 13.6, 6.8 Hz, 1H), 1.46 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H).

Step 3

N,N-diisopropyl-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **1d**

Compound **1c** (1.50 g, 5.28 mmol), potassium acetate (1.04 g, 10.6 mmol) and bis(pinacolato)diboron (2.01 g, 7.92 mmol) were dissolved in dioxane (20 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (386 mg, 527 μmol) was added, and the mixture was stirred at 100°C to allow for reacting for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the crude product of title Compound **1d** (790 mg).

MS m/z (ESI): 332.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 7.6 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.37 – 7.32 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 3.54 (s, 2H), 1.47 (d, J = 6.8 Hz, 6H), 1.25 (s, 12H), 1.10 – 1.05 (m, 6H).

Step 4

7-bromo-5-iodopyrrolo[2,1-f][1,2,4]triazin-4-amine **1f**

7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine **1e** (10.0 g, 46.9 mmol) was dissolved in *N,N*-dimethylformamide (500 mL), *N*-iodosuccinimide (11.6 g, 51.6 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (500 mL) and filtered under a reduced pressure to obtain a filter cake, which was the crude product of title Compound **1f** (13.7 g, 40.4 mmol, yield: 86.1%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.08 (s, 1H).

Step 5

2-{4-amino-7-bromopyrrolo[2,1-f][1,2,4]triazin-5-yl}-*N,N*-diisopropylbenzamide **1g**

Compound **1f** (8.0 g, 23.6 mmol) was dissolved in dimethyl sulfoxide (650 mL), *N,N*-dimethylformamide (100 mL) and water (70 mL). Sodium carbonate (5.00 g, 47.2 mmol), Compound **1d** (9.38 g, 28.3 mmol) and tetrakis(triphenylphosphine)palladium (1.36 g, 1.18 mmol) were added, and the mixture was stirred at 60°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, diluted with ethyl acetate (500 mL), and then washed with water (500 mL×3). The aqueous phase was extracted with ethyl acetate (500 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **1g** (3.32 g, 7.97 mmol, yield: 33.8%).

MS m/z (ESI): 416.0 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.54 – 7.43 (m, 2H), 7.39 (dd, J = 5.6, 2.8 Hz, 1H), 7.36 – 7.27 (m, 1H), 6.75 (s, 1H), 3.62 – 3.46 (m, 1H), 3.31 – 3.20 (m, 1H), 1.39 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 62.0 Hz, 6H), 0.27 (d, J = 41.6 Hz, 3H).

Step 6

5-(4-amino-5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl formate **1h**

Compound **1g** (450 mg, 1.08 mmol) and 5-(tetramethyl-1,3,2-dioxaboran-2-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl formate (401 mg, 1.30 mmol) were dissolved in dioxane (5.6 mL) and water (1.4 mL). Sodium carbonate (299 mg, 2.16 mmol) and tetrakis(triphenylphosphine)palladium (125 mg, 108 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **1h** (294 mg, 567 μmol, yield: 52.4%).

MS m/z (ESI): 519.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.49 (dd, J = 9.2, 5.6 Hz, 2H), 7.42 – 7.27 (m, 2H), 7.01 (s, 1H), 6.65 (s, 1H), 4.26 (s, 2H), 3.44 (d, J = 66.8 Hz, 6H), 2.31 (s, 3H), 1.45 – 1.37 (m, 12H), 1.00 (d, J = 73.2 Hz, 7H),

0.25 (s, 2H).

Step 7

3-(4-amino-5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-tert-butyl formate **1i**

Compound **1h**(294 mg, 567 μmol) was dissolved in acetic acid (4 mL), followed by the addition of PtO_2 (51.5 mg, 227 μmol). Under a hydrogen atmosphere, the mixture was stirred at room temperature for 12 hours. The mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **1i** (207 mg, 398 μmol, yield: 70.1%).

MS m/z (ESI): 521.25 [M+1]

Step 8

3-(5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-tert-butyl formate **1j**

Compound **1i** (207 mg, 567 μmol) was dissolved in tetrahydrofuran (5.0 mL) and cooled to 0°C, followed by the addition of tert-butyl nitrite (246 mg, 2.39 mmol), and the mixture was stirred at room temperature to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **1j** (36.0 mg, 71.2 μmol, yield: 17.9%).

MS m/z (ESI): 506.25 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.59 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.00 (d, *J* = 4.4 Hz, 1H), 5.76 (s, 1H), 4.07 (dd, *J* = 29.6, 6.4 Hz, 2H), 3.17 (d, *J* = 5.2 Hz, 3H), 2.97 – 2.82 (m, 1H), 2.08 (s, 1H), 1.83 – 1.66 (m, 2H), 1.53 (d, *J* = 16.0 Hz, 1H), 1.40 (d, *J* = 6.4 Hz, 12H), 1.08 (dd, *J* = 16.0, 6.4 Hz, 4H), 0.92 – 0.82 (m, 3H), 0.26 (t, *J* = 6.4 Hz, 3H).

Step 9

2-[7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-*N,N*-diisopropylbenzamide **1k**

At 0°C, Compound **1j** (15.0 mg, 29.7 μmol) was dissolved in methane dioxide (1.5 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature to allow for reacting for 3.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **1k** (12.0 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 406.1 [M+1]

Step 10

2-(7-{1-[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]piperidin-3-yl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)-*N,N*-diisopropylbenzamide **1**

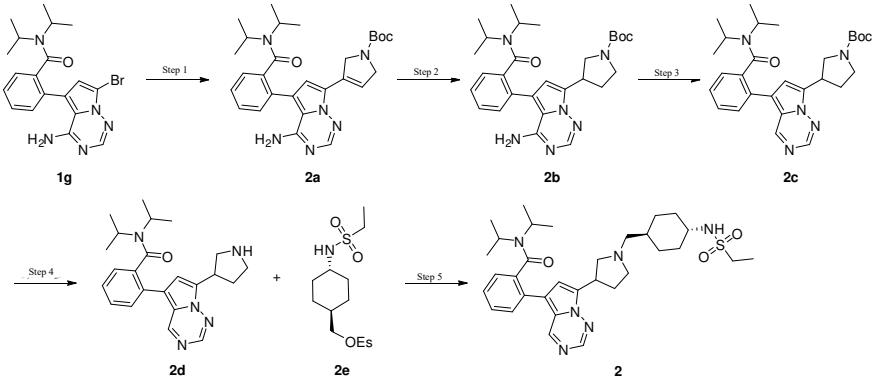
The crude product of Compound **1k** (12.0 mg), *N,N*-diisopropylethylamine (3.82 mg, 29.6 μmol) and 2-oxo-3*H*-1,3-benzoxazol-5-formaldehyde **1l** (5.79 mg, 35.5 μmol) were dissolved in dichloromethane (3 mL), and stirred at room temperature for 1.5 hours. The mixture was cooled to 0°C, sodium triacetoxyborohydride (31.4 mg, 148 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, the resulting residues were purified by the thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 45%-50%), to obtain the title Compound **1** (13.0 mg, 23.5 μmol, yield: 79.5%).

MS m/z (ESI): 553.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (d, *J* = 3.6 Hz, 1H), 8.54 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.17 (s, 1H), 7.05 –6.92 (m, 3H), 3.54 (s, 1H), 3.26 – 3.21 (m, 1H), 3.02 (s, 1H), 2.83 (s, 1H), 2.19 – 1.97 (m, 3H), 1.70 (s, 2H), 1.48 (s, 1H), 1.39 (t, *J* = 5.6 Hz, 3H), 1.23 (s, 1H),1.03 (dd, *J* = 25.6, 6.8 Hz, 3H), 0.91 – 0.78 (m, 3H), 0.22 (dd, *J* = 10.0, 6.8 Hz, 3H).

Example 2

N,N-diisopropyl-2-[7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzamide **2**



Step 1

3-(4-amino-5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **2a**

Compound **1g** (450 mg, 1.08 mmol) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (382 mg, 1.30 mmol) were dissolved in dioxane (4.0 mL) and water (1.0 mL). Potassium carbonate (299 mg, 2.16 mmol) and tetrakis(triphenylphosphine)palladium (124 mg, 108 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **2a** (334 mg, 661 μmol, yield: 61.2%).

MS m/z (ESI): 505.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.53 – 7.44 (m, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 6.65 (d, J = 14.8 Hz, 1H), 4.37 (d, J = 74.4 Hz, 4H), 3.58 (s, 1H), 3.28 (s, 1H), 1.49 – 1.33 (m, 12H), 0.99 (d, J = 62.4 Hz, 7H), 0.23 (s, 2H).

Step 2

3-(4-amino-5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidin-1-tert-butyl formate **2b**

Compound **2a** (334 mg, 661 μmol) was dissolved in acetic acid (5 mL), followed by the addition of PtO_2 (60.1 mg, 264 μmol). Under a hydrogen atmosphere, the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **2b** (335 mg, 661 μmol, yield: 99.9%).

MS m/z (ESI): 507.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.51 – 7.41 (m, 2H), 7.36 (d, J = 6.8 Hz, 1H), 7.30 (d, J = 6.4 Hz, 1H), 6.53 (s, 1H), 3.82 (s, 2H), 3.44 (dd, J = 14.0, 6.8 Hz, 1H), 3.39 – 3.20 (m, 4H), 2.27 (dd, J = 21.2, 16.0 Hz, 1H), 2.07 – 1.90 (m, 1H), 1.86 (s, 2H), 1.40 (d, J = 12.0 Hz, 12H), 1.17 – 0.76 (m, 7H), 0.24 (s, 2H).

Step 3

3-(5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidin-1-tert-butyl formate **2c**

Compound **2b**(230 mg, 453 μmol) and 2-hydroxylbenzoic acid (6.27 mg, 45.4 μmol) were dissolved in tetrahydrofuran (4.6 mL) and cooled to 0°C, followed by the addition of tert-butyl nitrite (280 mg, 2.72 mmol), and the mixture was stirred at room temperature to allow for reacting for 1.0 hour, warmed to 60°C and stirred to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, and the residues were purified by the preparative thin-layer chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the title Compound **2c** (63.0 mg, 128 μmol, yield: 28.2%).

MS m/z (ESI): 492.3 [M+1]

Step 4

N,N-diisopropyl-2-[7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzamide **2d**

At 0°C, Compound **2c** (60.0 mg, 122 μmol) was dissolved in methane dioxide (0.75 mL) and trifluoroacetic acid (0.25 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **2d**, which was directly used in the next step of reaction without purification.

MS m/z (ESI): 392.2 [M+1]

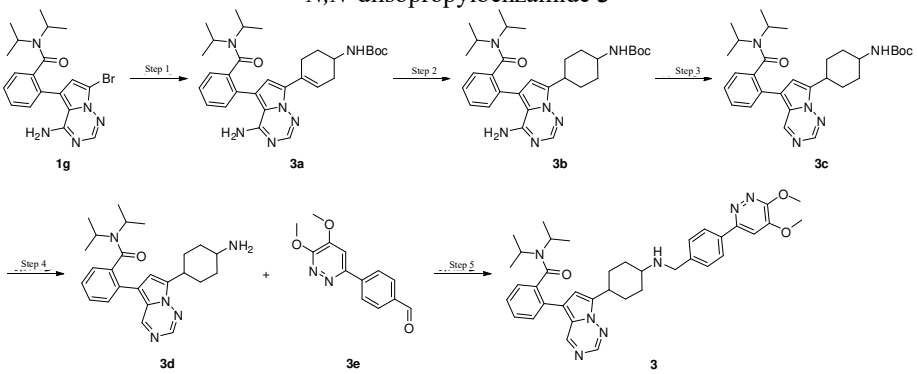
Step 5

N,N-diisopropyl-2-[7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzamide **2**

The crude product of Compound **2d** (50.0 mg) and [(1r,4r)-4-ethanesulfonamidocyclohexyl]methylethan-1-sulfonate **2e** (22.5 mg, 72 μmol) were dissolved in *N,N*-dimethylformamide (1 mL), followed by the addition of potassium carbonate (26.5 mg, 192 μmol) and potassium iodide (7.97 mg, 48.0 μmol), and the mixture was stirred at 80°C for 12 hours. The reaction mixture was concentrated under a reduced pressure, the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 35%-45%), to obtain the title Compound **2** (9.7 mg, 16.3 μmol, yield: 33.9 %).
MS m/z (ESI): 595.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 2.4 Hz, 1H), 8.56 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 3.2 Hz, 1H), 7.00 (dd, J = 7.6, 3.2 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.28 (d, J = 7.2 Hz, 2H), 3.06 – 2.89 (m, 4H), 2.66 (q, J = 8.0 Hz, 1H), 2.40 – 2.15 (m, 4H), 1.83 (d, J = 12.4 Hz, 5H), 1.41 (dd, J = 6.4, 1.6 Hz, 3H), 1.36 – 1.07 (m, 10H), 0.87 (d, J = 6.8 Hz, 5H), 0.25 (dd, J = 6.8, 2.4 Hz, 3H).

Example 3

2-{7-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]pyrrolo[2,1-f][1,2,4] triazin-5-yl}-*N,N*-diisopropylbenzamide **3**



Step 1

N-[4-(4-amino-5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate **3a**

Compound **1g** (500 mg, 1.20 mmol) and *N*-[4-(tetramethyl-1,3,2-dioxaboran-2-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate (466 mg, 1.44 mmol) were dissolved in dioxane (8.0 mL) and water (2.0 mL). Potassium carbonate (332 mg, 2.40 mmol) and tetrakis(triphenylphosphine)palladium (138.8 mg, 120.1 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the resulting crude product is triturated with ethyl acetate (20 mL) for purification, to obtain the title Compound **3a** (490 mg, 920 μmol, yield: 76.5%).
MS m/z (ESI): 533.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.51 – 7.43 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.94 – 6.79 (m, 2H), 6.64 (s, 1H), 3.52 (s, 2H), 3.26 (s, 1H), 2.64 – 2.53 (m, 1H), 2.42 (s, 1H), 2.20 – 2.06 (m, 1H), 1.90 (d, J = 8.4 Hz, 1H), 1.62 – 1.48 (m, 1H), 1.40 (s, 13H), 1.21 – 0.10 (m, 8H).

Step 2

N-[4-(4-amino-5-{2-[bdiisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexyl]tert-butyl carbamate **3b**

Compound **3a** (440 mg, 826 μmol) was dissolved in acetic acid (10 mL), followed by the addition of PtO_2 (75.0 mg, 330 μmol). Under a hydrogen atmosphere (1.5 Mpa), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **3b** (433mg, 810 μmol, yield: 98.0%).
MS m/z (ESI): 535.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 3.6 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 6.92 – 6.75 (m, 1H), 6.65 – 6.40 (m, 1H), 3.64 – 3.49 (m, 1.43H), 3.31 – 3.21 (m, 2H), 3.04 – 2.96 (m, 0.56H), 2.09 – 1.52 (m, 7H), 1.38 (s, 12H), 1.34 – 1.29 (m, 1H), 1.19 – 0.77 (m, 7H), 0.24 (s, 2H).

Step 3

N-[4-(5-{2-[diisopropylaminoformyl]phenyl}pyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexyl]tert-butyl carbamate **3c**

Compound **3b** (353 mg, 660 μmol) and 2-hydroxylbenzoic acid (9.12 mg, 66.0 μmol) were dissolved in tetrahydrofuran (10.0 mL) and cooled to 0°C, followed by the addition of tert-butyl nitrite (408 mg, 3.96 mmol). The

mixture was warmed to 70°C and stirred to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the title Compound **3c** (140 mg, 269 μmol, yield: 40.8%).
MS m/z (ESI): 520.3 [M+1]

Step 4

2-[7-(4-aminocyclohexyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-*N,N*-diisopropyl)benzamide **3d**

At 0°C, Compound **3c** (120 mg, 231 μmol) was dissolved in methane dioxide (4.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **3d**, which was directly used in the next step of reaction without purification.
MS m/z (ESI): 420.2 [M+1]

Step 5

2-{7-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]pyrrolo[2,1-f][1,2,4] triazin-5-yl}-*N,N*-diisopropylbenzamide **3**

Compound **3d** (49.0 mg, 117 μmol) and 4-(5,6-dimethoxypyridazin-3-yl)benzaldehyde **3e**(28.5 mg, 117 μmol) were dissolved in dichloromethane (5 mL), and the mixture was stirred at 0°C for 0.5 hours. Sodium triacetoxyborohydride (124 mg, 584 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.05% ammonia water), elution gradient: 45%-90%), to obtain the title Compound **3** (2.51 mg, 3.87 μmol, yield: 3.31%).
MS m/z (ESI): 648.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.54 (s, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.54 – 7.41 (m, 4H), 7.30 (d, J = 7.2 Hz, 1H), 7.01 (s, 1H), 4.05 (s, 3H), 3.98 (s, 3H), 3.78 (s, 2H), 3.41 – 3.38 (m, 1H), 3.27 – 3.24 (m, 1H), 2.86 (s, 1H), 2.03 – 1.57 (m, 10H), 1.40 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.27 (d, J = 6.4 Hz, 3H).

Example 4

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl-1-ene-1-yl]pyrrolo[1,2-a]pyrazin-8-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **4**

Step 1

2-bromo-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **4b**

N-ethylprop-2-amine (12 g, 137.67 mmol) and triethylamine (27.72 g, 273.96 mmol) were added to the solution of 2-bromo-5-fluoro-benzoic acid **4a** (20 g, 91.32 mmol) in dichloromethane (250 mL), followed by the slow addition of HATU (52.08 g, 136.98 mmol). The mixture was stirred at 25°C for 12 hours. The mixture was washed with a saturated aqueous sodium carbonate solution (100 mL×3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain a crude product, which was purified by the silica-gel column chromatography (A: petroleum ether, B: ethyl acetate, 0% B to 15% B at A, TLC (petroleum ether :ethyl acetate =1:1, Rf=0.35)), to obtain the title Compound **4b** (24 g, 83.29 mmol, yield91.20%) as white solid.
MS m/z (ESI): 289.8 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 – 7.61 (m, 1H), 7.38 – 7.29 (m, 1H), 7.22 (dt, J = 3.0, 8.6 Hz, 1H), 3.57 – 3.38 (m, 2H), 3.26 (qd, J = 7.0, 13.8 Hz, 1H), 1.25 – 1.17 (m, 6H), 1.06 (d, J = 6.6 Hz, 2H), 0.96 (t, J = 7.1 Hz, 1H)

Step 2

N-ethyl-5-fluoro-N-isopropyl-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **4c**

Compound **4b** (13 g, 45.11 mmol), potassium acetate (13.3 g, 135.52 mmol) and bis(pinacolato)diboron (35 g, 137.83 mmol) were dissolved in DMSO(200 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2.DCM (3.30 g, 4.51 mmol) was added, and the mixture was stirred at 110°C to allow for reacting for 12 hours. After the mixture was cooled to room temperature, 100 mL of water was added, and the mixture was extracted with ethyl acetate (150ml × 3). The organic

layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain a crude product, which was purified by the silica-gel column chromatography purified (A: petroleum ether, B:ethyl acetate, 0% B to 20% B at A, TLC (petroleum ether :ethyl acetate =3:1, Rf=0.2)), to obtain the title Compound **4c** (10 g, 29.83 mmol, yield: 66.12%).
MS m/z (ESI): 336.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (dd, J = 6.5, 8.1 Hz, 1H), 7.20 (dt, J = 2.4, 8.7 Hz, 1H), 7.09 (br dd, J = 2.4, 9.4 Hz, 1H), 3.54 (td, J = 6.6, 13.2 Hz, 1H), 3.31 – 3.27 (m, 2H), 1.28 – 1.20 (m, 16H), 1.16 (s, 4H)

Step 3

6,8-dibromopyrrolo[1,2-a]pyrazine **4e**

Pyrrolo[1,2-a]pyrazine **4d** (2.0 g, 16.93 mmol) was dissolved in dichloromethane (80 mL), followed by the addition of *N*-bromosuccinimide (6.03 g, 33.86 mmol), and the mixture was stirred at 25°C for 2 hours. The reaction mixture was quenched by adding water (20 mL), and extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to obtain the crude product of title Compound **4e** (4.0 g, 14.5 mmol, yield: 85.63%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 276.9 [M+1].

Step 4

N-(4-{8-bromopyrrolo[1,2-a]pyrazin-6-yl}cyclohexyl-3-ene-1-yl)tert-butyl carbamate **4f**

Compound **4e** (1.5 g, 5.44 mmol) and *N*-[4-(tetramethyl-1,3,2-dioxaboran-2-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate (1.50 g, 4.64 mmol) were dissolved in dioxane (20 mL) and water (2.0 mL). Sodium carbonate (1.20 g, 11.32 mmol) and a 1,1-bis(diphenylphosphino)ferrocene palladium (II) dichloride dichloromethane complex (225.00 mg, 275.52 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (30 mL×3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **4f** (900 mg, 2.29 mmol, yield: 42.2%).
MS m/z (ESI): 393.9 [M+1]

Step 5

N-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate **4g**

Compound **4f** (900 mg, 2.29 mmol) and Compound **4c**(1.15 g, 3.44 mmol) were dissolved in dioxane (15 mL) and water (1.5 mL). Sodium carbonate (730 mg, 6.89 mmol) and a 1,1-bis(diphenylphosphino)ferrocene palladium (II) dichloride dichloromethane complex (150 mg, 230.15 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **4g** (600 mg, 1.15 mmol, yield: 50.23%).
MS m/z (ESI): 521.2 [M+1]

Step 6

2-[6-(4-aminocyclohexyl-1-ene-1-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **4h**

Compound **4g** (170 mg, 326.52 μmol) was dissolved in methane dioxide (4.94 mL), followed by the addition of trifluoroacetic acid (372.3 mg, 3.27 mmol, 0.25 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **4h** (220 mg), which was directly used in the next step of reaction without purification.

Step 7

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl-1-ene-1-yl]pyrrolo[1,2-a]pyrazin-8-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **4**

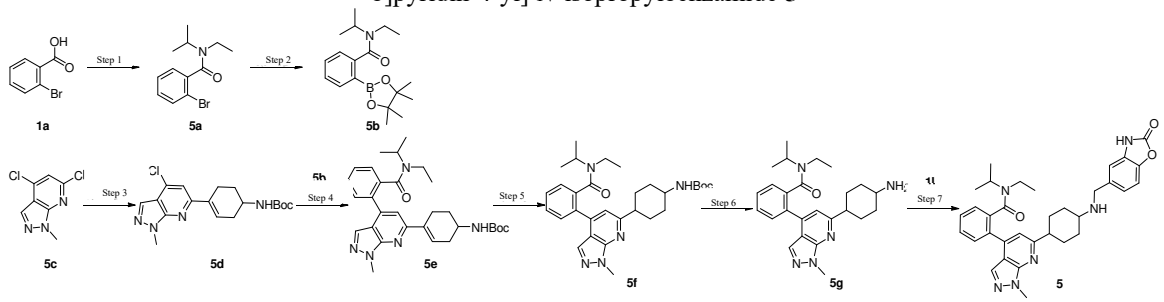
The crude product of Compound **4h** (140 mg) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (265.02 mg, 2.62 mmol) and Compound **3e**(51.18 mg, 209.52 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (49.38 mg, 785.72 μmol) was added, and the mixture was stirred at 45°C for 12 hours. The reaction mixture was cooled to room temperature, diluted with a saturated aqueous sodium bicarbonate solution (20 mL), and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 8%-38%), to obtain the title Compound **4** (79.75 mg, 122.93 μmol, yield: 46.9%).

MS m/z (ESI): 649.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.25 (d, J=5.2 Hz, 1H), 8.05 (d, J=8.4 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.55 – 7.47 (m, 3H), 7.37 – 7.21 (m, 2H), 6.85 – 6.80 (m, 1H), 6.07 (s, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.87 (s, 2H), 2.92 – 2.77 (m, 2H), 2.58 (s, 1H), 2.45 – 2.22 (m, 4H), 2.12 – 1.98 (m, 2H), 1.64 – 1.48 (m, 1H), 1.26 – 1.01 (m, 1H), 0.89 – 0.85 (m, 2H), 0.82 – 0.74 (m, 3H), 0.73 – 0.65 (m, 1H), 0.28 – 0.16 (m, 3H).

Example 5

N-ethyl-2-[1-methyl-6-(4-{[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]amino}cyclohexyl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-isopropylbenzamide **5**



Step 1

2-bromo-*N*-ethyl-*N*-isopropylbenzamide **5a**

Compound **1a** (5.00 g, 24.8 mmol), isopropylethylamine (2.60 g, 29.8 mmol, 3.61 mL), HOBt (4.03 g, 29.8 mmol) and diisopropylethylamine (6.43 g, 49.7 mmol, 8.67 mL) were dissolved in dichloromethane (50 mL), and cooled to 0°C, followed by the addition of EDCI (5.72 g, 29.8 mmol), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the title Compound **5a** (6.29 g, 23.2 mmol, yield: 93.6%).

MS m/z (ESI): 269.9 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 – 7.63 (m, 1H), 7.48 – 7.42 (m, 1H), 7.37 – 7.29 (m, 2H), 4.57 – 4.46 (m, 0.27H), 3.55 – 3.40 (m, 1.42H), 3.32 – 3.22 (m, 0.72H), 3.19 – 3.09 (m, 0.27H), 2.98 – 2.88 (m, 0.26H), 1.28 – 1.15 (m, 6H), 1.08 – 0.90 (m, 3H).

Step 2

N-ethyl-*N*-isopropyl-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **5b**

Compound **5a** (3.00 g, 11.1 mmol), potassium acetate (2.18 g, 22.2 mmol) and bis(pinacolato)diboron (4.23 g, 16.6 mmol) were dissolved in dioxane (40 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2(812 mg, 1.11 mmol) was added, and the mixture was stirred at 100°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, diluted with water (120 mL), and extracted with ethyl acetate (120 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the crude product of title Compound **5b** (1.51 g). The crude product was directly used in the next step of reaction.

Step 3

N-(4-{4-chloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl}cyclohexyl-3-ene-1-yl)tert-butyl carbamate **5d**

4,6-dichloro-1-methyl-1H-pyrazolo[3,4-b]pyridine **5c**(500 mg, 2.47 mmol) and *N*-[4-(tetramethyl-1,3,2-dioxaboran-2-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate (640 g, 1.98 mmol) were dissolved in dioxane (6.0 mL) and water (1.2 mL). Sodium carbonate (524 mg, 4.95 mmol) and 1,1-bis(diphenylphosphino)ferrocene palladium (II) dichloride (181 mg, 247 μmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **5d** (360 mg, 0.99 mmol, yield: 40.1%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.58 (s, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 4.05 (s, 3H), 3.57 (s, 1H), 2.83 (d, J = 17.6 Hz, 1H), 2.54 (s, 1H), 2.48 – 2.45 (m, 1H), 2.16 (dd, J = 17.2, 8.8 Hz, 1H), 1.95 (d, J = 11.8 Hz, 1H), 1.58 (tt, J = 10.8, 5.2 Hz, 1H), 1.40 (s, 9H).

Step 4

N-[4-(4-{2-[ethyl(isopropyl)aminoformyl]-phenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate **5e**

Compound **5d** (350 mg, 0.96 mmol) and Compound **5b**(336 mg, 1.06 mmol) were dissolved in dioxane (6.0 mL) and water (1.2 mL). Sodium carbonate (204 mg, 1.93 mmol) and 1,1-bis(diphenylphosphino)ferrocene palladium (II)

dichloride (70.6 mg, 96 μmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **5e** (380 mg, 0.73 mmol, yield: 75.2%).

MS m/z (ESI): 518.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.9 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.63 – 7.56 (m, 2H), 7.48 – 7.42 (m, 1H), 7.38 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.67 (s, 1H), 4.06 (d, J = 2.4 Hz, 3H), 3.55 (s, 1H), 3.36 (dd, J = 12.8, 6.4 Hz, 3H), 2.79 (d, J = 39.2 Hz, 2H), 2.17 (s, 1H), 1.99 – 1.93 (m, 1H), 1.64 – 1.50 (m, 1H), 1.40 (s, 9H), 0.84 (dd, J = 6.4, 4.0 Hz, 6H), 0.67 (d, J = 6.8 Hz, 3H).

Step 5

N-[4-(4-{2-[ethyl(isopropyl)aminoformyl]-phenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)cyclohexyl]tert-butyl carbamate **5f**

Compound **5e** (380 mg, 734 μmol) was dissolved in methanol (5 mL), followed by the addition of Pd/C (10 wt.% 50% water, 8.92 mg, 73.4 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **5f** (300 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 520.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 11.6 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.44 (d, J = 6.0 Hz, 1H), 7.22 – 7.07 (m, 1H), 6.96 – 6.76 (m, 1H), 4.05 (d, J = 3.2 Hz, 3H), 3.40 (d, J = 17.2 Hz, 1H), 2.88 (dd, J = 21.6, 7.6 Hz, 1H), 2.77 – 2.65 (m, 1H), 2.51 (s, 2H), 1.91 (s, 3H), 1.80 – 1.55 (m, 4H), 1.39 (d, J = 1.2 Hz, 9H), 0.86 (d, J = 6.4 Hz, 3H), 0.79 – 0.65 (m, 6H).

Step 6

2-[6-(4-aminocyclohexyl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-ethyl-*N*-isopropylbenzamide **5g**

Compound **5f** (300 mg, 577 μmol) was dissolved in methane dioxide (6.0 mL), followed by the addition of trifluoroacetic acid (0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **5g** (245 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 420.3 [M+1]

Step 7

N-ethyl-2-[1-methyl-6-(4-{[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]amino}cyclohexyl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-isopropylbenzamide **5**

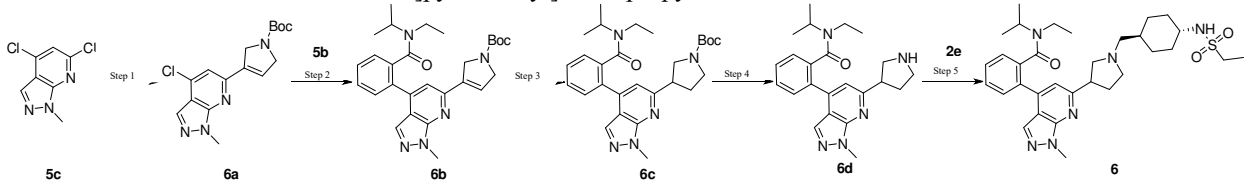
The crude product of Compound **5g** (80 mg, 191 μmol) was dissolved in dichloromethane (1.0 mL), followed by the addition of triethylamine to regulate the PH value of the reaction mixture to 9-10, followed by the addition of Compound **1l** (31.1 mg, 191 μmol) and sodium triacetoxyborohydride (121 mg, 572 μmol) at 0°C, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 5%-50%), to obtain the title Compound **5** (62.6 mg, 110 μmol, yield: 58.0 %).

MS m/z (ESI): 567.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (d, J = 9.2 Hz, 1H), 8.67 (d, J = 66.0 Hz, 2H), 7.98 (d, J = 4.8 Hz, 1H), 7.65 – 7.42 (m, 4H), 7.41 – 7.10 (m, 4H), 4.23 (d, J = 5.2 Hz, 2H), 4.07 (d, J = 14.8 Hz, 3H), 3.42 – 2.70 (m, 5H), 2.30 – 1.49 (m, 8H), 1.09 – 0.13 (m, 9H).

Example 6

N-ethyl-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-N-isopropylbenzamide **6**



Step 1

3-{4-chloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **6a**

4,6-Dichloro-1-methyl-1H-pyrazolo[3,4-b]pyridine **5c** (200 mg, 989 μmol) was dissolved in dioxane (3.0 mL) and water (0.6 mL). Sodium carbonate (209 mg, 1.98 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (233 mg, 791.9 μmol) and Pd(dppf)Cl_2(72.4 mg, 98.9 μmol) were added, and the mixture

was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **6a** (150 mg, 448 μmol, yield: 45.2%).
MS m/z (ESI): 279.1 [M-55]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 12.8 Hz, 1H), 4.54 (s, 2H), 4.32 (s, 2H), 4.06 (d, J = 1.2 Hz, 3H), 1.46 (d, J = 8.8 Hz, 9H).

Step 2

3-(4-{2-[ethyl(isopropyl)aminoformyl]-phenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **6b**

Compound **6a** (130 mg, 388 μmol) and Compound **5b** (184 mg, 582 μmol) were dissolved in dioxane (3.0 mL) and water (0.6 mL). Sodium carbonate (204 mg, 1.93 mmol) and 1,1-bis(diphenylphosphino)ferrocene palladium (II) dichloride (70.6 mg, 96 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **6b** (60 mg, 122.5 μmol, yield: 31.5%).

Step 3

3-(4-{2-[ethyl(isopropyl)aminoformyl]-phenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **6c**

Compound **6b** (60 mg, 122.5 μmol) was dissolved in methanol (2.0 mL), followed by the addition of Pd/C (6.0 mg). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **6c** (53.0 mg, 107 μmol, yield: 87.9%).
MS m/z (ESI): 492.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.61 (dd, J = 10.4, 6.4 Hz, 3H), 7.46 (dd, J = 12.0, 6.4 Hz, 1H), 7.14 (s, 1H), 4.05 (s, 3H), 3.76 – 3.36 (m, 5H), 2.89 (s, 1H), 2.25 (s, 1H), 2.20 – 2.11 (m, 1H), 1.41 (d, J = 4.8 Hz, 9H), 0.90 – 0.14 (m, 9H).

Step 4

N-ethyl-2-[1-methyl-6-(pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-isopropylbenzamide **6d**

Compound **6c** (47.0 mg, 95.6 μmol) was dissolved in methane dioxide (4.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **6d** (38 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 392.3 [M+1]

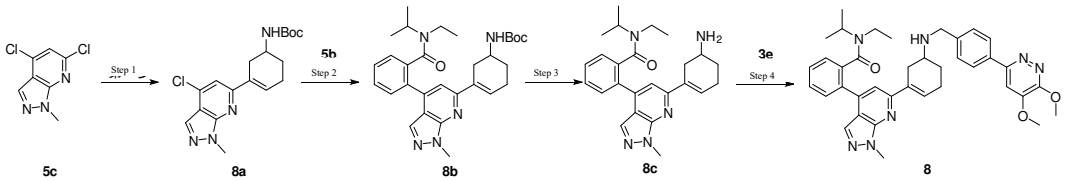
Step 5

N-ethyl-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-N-isopropylbenzamide **6**

The crude product of Compound **6d** (38.0 mg, 97.0 μmol) and [(1r,4r)-4-ethanesulfonamidocyclohexyl]methylethan-1-sulfonate **2e**(45.8 mg, 97.0 μmol) were dissolved in *N,N*-dimethylformamide (2.0 mL), followed by the addition of potassium carbonate (53.6 mg, 388 μmol) and potassium iodide (16.1 mg, 97.0 μmol), and the mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated under a reduced pressure, the residues were purified by the preparative thin-layer chromatography, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 55%-40%), to obtain the title Compound **6** (13.0 mg, 21.8 μmol, yield: 22.5%) as white solid.
MS m/z (ESI): 595.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.62 – 7.54 (m, 3H), 7.42 (d, J = 4.4 Hz, 1H), 7.16 (s, 1H), 4.05 (s, 3H), 3.71 – 3.60 (m, 1H), 3.42 (d, J = 6.8 Hz, 1H), 3.22 – 2.71 (m, 9H), 2.47 (d, J = 12.4 Hz, 1H), 2.29 (s, 2H), 2.18 – 2.07 (m, 1H), 1.94 – 1.79 (m, 4H), 1.42 (d, J = 20.8 Hz, 1H), 1.33 – 0.06 (m, 17H).

Example 8

2-{6-[5-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl-1-ene-1-yl]1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-*N*-isopropylbenzamide **8**



Step 1

N-(3-{4-chloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl}cyclohexyl-3-ene-1-yl)tert-butyl carbamate **8a**

4,6-Dichloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridine **5c** (300 mg, 1.48 mmol) was dissolved in dioxane (12 mL) and water (2.0 mL). Sodium carbonate (315 mg, 2.97 mmol) , *N*-[3-(tetramethyl-1,3,2-dioxaboran-2-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate (504 mg, 1.56 mmol) and Pd(dppf)Cl_2 (109 mg, 149 μmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **8a** (220 mg, 606 μmol, yield: 40.8%) as white solid.

MS m/z (ESI): 363.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.57 (s, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.86 (s, 1H), 4.04 (s, 3H), 3.62 (s, 1H), 2.93 (d, J = 15.6 Hz, 1H), 2.32 (dd, J = 16.8, 10.4 Hz, 3H), 1.83 (d, J = 12.4 Hz, 1H), 1.58 – 1.39 (m, 10H).

Step 2

N-[3-(4-{2-[ethyl(isopropyl)aminoformyl]phenyl}-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate **8b**

Compound **8a** (250 mg, 689 μmol) and sodium carbonate (146 mg, 1.38 mmol) were dissolved in dioxane (6.0 mL) and water (1.0 mL). Compound **5b** (437 mg, 689 μmol) and 1,1-bis(diphenylphosphino)ferrocene palladium (II) dichloride (50.4 mg, 68.9 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **8b** (227 mg, 439 μmol, yield: 63.7%).

MS m/z (ESI): 518.3 [M+1]

Step 3

2-[6-(5-aminocyclohexyl-1-ene-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-ethyl-*N*-isopropylbenzamide **8c**

Compound **8b** (90.0 mg, 174 μmol) was dissolved in methane dioxide (2.1 mL), followed by the addition of trifluoroacetic acid (0.7 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **8c** (72 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 418.3 [M+1]

Step 4

2-{6-[5-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl-1-ene-1-yl]1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-*N*-isopropylbenzamide **8**

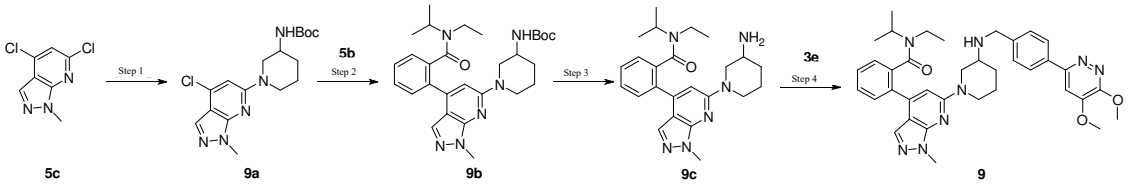
The crude product of Compound **8c** (72 mg, 172 μmol) was dissolved in dichloromethane (4.0 mL), followed by the addition of Compound **3e** (42 mg, 172 μmol). The mixture was cooled to 0°C, sodium triacetoxyborohydride (183 mg, 862 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 50%-90%), to obtain the title Compound **8** (20.3 mg, 31.4 μmol, yield: 14.7 %).

MS m/z (ESI): 646.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.8 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.51 (m, 5H), 7.49 – 7.42 (m, 1H), 7.38 (d, J = 4.0 Hz, 1H), 6.71 (s, 1H), 4.29 – 4.19 (m, 0.23 H), 4.05 (s, 6H), 3.98 (s, 3H), 3.92 (s, 2H), 3.40 – 3.35 (m, 1H), 3.01 (dd, J = 37.2, 16.0 Hz, 1H), 2.89 – 2.69 (m, 2H), 2.44 – 2.18 (m, 4H), 1.97 (d, J = 11.2 Hz, 1H), 1.41 (d, J = 6.8 Hz, 1H), 1.08 – 0.61 (m, 7H), 0.17 (d, J = 6.4 Hz, 2H).

Example 9

2-{6-[3-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-*N*-isopropylbenzamide **9**



Step 1

N-(1-{4-chloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl}piperidin-3-yl)tert-butyl carbamate **9a**

4,6-Dichloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridine **5c** (300 mg, 1.48 mmol) and *N*-(piperidin-3-yl)tert-butyl carbamate (297 mg, 1.48 mmol) were dissolved in toluene (6 mL). $Pd_2(dba)_3$ (85.3 mg, 148 μmol), BINAP (184 mg, 296 μmol) and K_2CO_3 (410 mg, 2.97 mmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **9a** (60.0 mg, 164 μmol, yield: 11%) as colorless oil.

MS m/z (ESI): 366.1 [M+1]

Step 2

N-[1-(4-{2-[ethyl(isopropyl)aminoformyl]phenyl}-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)piperidin-3-yl]tert-butyl carbamate **9b**

Compound **9a** (55.0 mg, 150 μmol) and Compound **5b** (95.3 mg, 300 μmol) were dissolved in dioxane (4.0 mL) and water (1.0 mL). Xphos-Pd-G2 (11.8 mg, 15.0 μmol), Xphos (14.3 mg, 30.0 μmol) and Cs_2CO_3 (97.9 mg, 300 μmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **9b** (64.0 mg, 122 μmol, yield: 81.7%).

MS m/z (ESI): 521.3 [M+1]

Step 3

2-[6-(3-aminopiperidin-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-ethyl-*N*-isopropylbenzamide **9c**

Compound **9b** (50.0 mg, 96 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **9c** (40 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 421.2 [M+1]

Step 4

2-{6-[3-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-*N*-isopropylbenzamide **9**

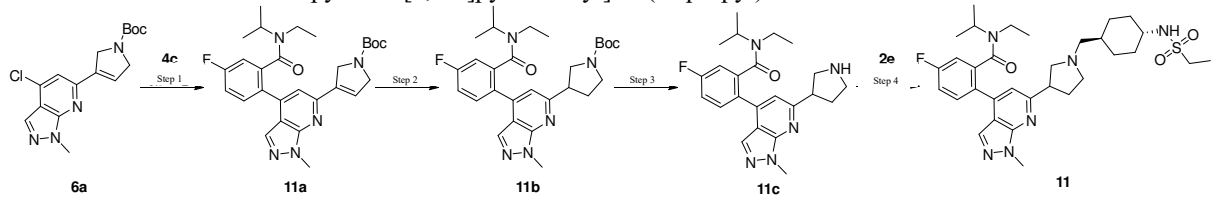
The crude product of Compound **9c** (40 mg, 95.1 μmol) was dissolved in dichloromethane (2.5 mL), followed by the addition of Compound **3e** (23.2 mg, 95.1 μmol). The mixture was cooled to 0°C, sodium triacetoxyborohydride (141 mg, 665 μmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 5%-50%), to obtain the title Compound **9** (26.0 mg, 40 μmol, yield: 42.1 %) as white solid.

MS m/z (ESI): 649.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 – 7.83 (m, 2H), 7.74 – 7.25 (m, 8H), 6.78 – 6.63 (m, 1H), 4.50 – 4.39 (m, 1H), 4.28 – 4.11 (m, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.91 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 3.13 – 2.62 (m, 5H), 1.98 (s, 1H), 1.74 (s, 1H), 1.39 (s, 2H), 1.14 – 0.55 (m, 7H), 0.31 – 0.14 (m, 2H).

Example 11

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-(isopropyl)benzamide **11**



Step 1

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **11a**

Compound **6a** (100 mg, 299 μmol) and Compound **4c** (215 mg, 448 μmol) were dissolved in dioxane (8.0 mL) and water (2.0 mL). Sodium carbonate (63.3 mg, 597 μmol) and Pd(dppf)Cl_2 (21.8 mg, 29.8 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **11a** (97.0 mg, 191 μmol, yield: 63.9%) as white solid.

MS m/z (ESI): 508.2 [M+1]

Step 2

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **11b**

Compound **11a** (97.0 mg, 191 μmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (10 mg). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **11b** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 510.2 [M+1]

Step 3

N-ethyl-5-fluoro-2-[1-methyl-6-(pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-isopropylbenzamide **11c**

Compound **11b** (50.0 mg, 98.1 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.4 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **11c** (40 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 410.2 [M+1]

Step 5

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-(isopropyl)benzamide **11**

The crude product of Compound **11c** (40mg) and [(1r,4r)-4-ethanesulfonamidocyclohexyl]methylethan-1-sulfonate **2e** (166 mg, 352 μmol) were dissolved in *N,N*-dimethylformamide (6.0 mL), followed by the addition of potassium carbonate (162 mg, 1.17 mmol) and potassium iodide (48.6 mg, 293 μmol), and the mixture was stirred at 80°C for 16 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 5%-60%), to obtain the title Compound **11** (70.0 mg, 114 μmol, yield: 38.9 %) as white solid.

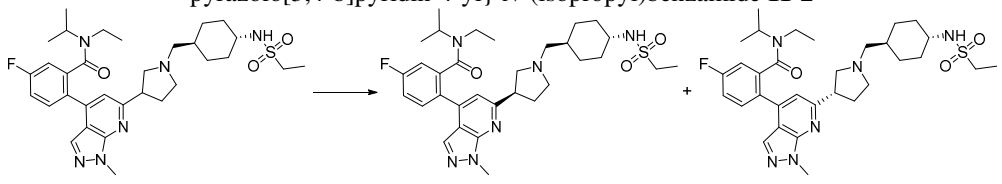
MS m/z (ESI): 613.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.68 (dd, J = 8.4, 5.2 Hz, 1H), 7.48 – 7.33 (m, 2H), 7.13 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.04 (s, 3H), 3.63 – 3.56 (m, 2H), 3.08 – 2.62 (m, 10H), 2.40 – 2.01 (m, 4H), 1.84 (s, 4H), 1.54 – 0.06 (m, 18H).

Examples 11-1 and 11-2

N-ethyl-5-fluoro-2-{1-methyl-6-[(3R)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-(isopropyl)benzamide **11-1**

N-ethyl-5-fluoro-2-{1-methyl-6-[(3S)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-(isopropyl)benzamide **11-2**



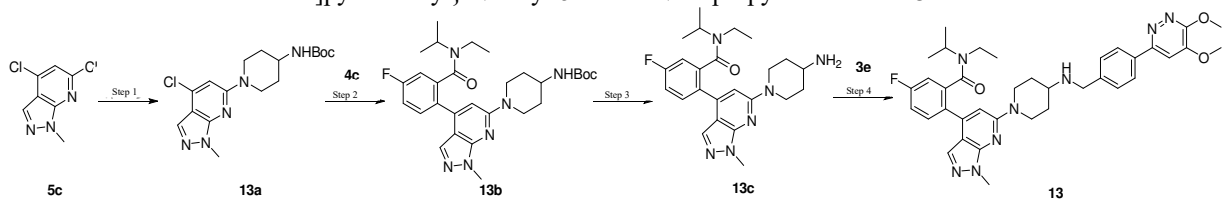
11 **11-1** **11-2**

Racemic Compound **11** (68 mg, 111 μmol) was purified by the chiral preparative SFC (chiral preparative column: CHIRALCEL AD (250 mm * 30 mm, 10 um); mobile phase: n-hexane/isopropanol/diethylamine = 70/30/0.1 (V/V/V)), and the corresponding components were collected and concentrated under a reduced pressure. The obtained respective components were respectively purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 10%-35%), to obtain the title Compounds **11-1** (12 mg, 0.02 mmol, yield: 17.6%) and **11-2** (7.0 mg, 0.01 mmol, yield: 10.2%).

Single-configuration Compound 11-1:
MS m/z (ESI):613.2 [M+1]
Chiral SFC analysis: retention time: 2.310 min; chromatographic column: DAICEL AD-H 4.6 mm I.D.*250 mm L 5 μm; mobile phase: CO_2/IPA[0.1% NH_3 (7M methanol solution)] = 60/40.
1H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 2.8 Hz, 1H), 7.67 (dt, J = 9.2, 4.8 Hz, 1H), 7.50 – 7.33 (m, 2H), 7.13 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.25 – 4.13(m, 0.25H), 4.04 (d, J = 2.0 Hz, 3H), 3.62 – 3.49 (m, 1.78H), 3.05 – 2.56 (m, 9H), 2.36 – 2.16 (m, 3H), 2.08 (s, 1H), 1.83 (t, J = 17.2 Hz, 4H), 1.42 – 1.28 (m,1H), 1.27 – 1.13 (m, 5H), 1.06 – 0.65 (m, 9H), 0.21 (t, J = 6.0 Hz, 2H).
Single-configuration Compound 11-2:
MS m/z (ESI):613.2 [M+1]
Chiral SFC analysis: retention time: 2.425 min; chromatographic column: DAICEL AD-H 4.6 mm I.D.*250 mm L 5 μm; mobile phase: CO_2/IPA[0.1% NH_3 (7M methanol solution)] = 60/40.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 1H), 7.46 (s, 1H), 7.31 – 7.10 (m, 2H), 6.92 (s, 1H), 6.80 (d, J = 6.4 Hz, 1H), 4.03 – 3.94 (m, 0.47H), 3.83 (s, 3H), 3.48 –3.37 (m, 1.62H), 2.85 – 2.67 (m, 5H), 2.60 – 2.38 (m, 4H), 2.19 – 1.48 (m, 9H), 1.23 – 0.40 (m, 16H).

Example 13

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **13**



Step 1

N-(1-{4-chloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl}piperidin-4-yl)tert-butyl carbamate **13a**

4,6-Dichloro-1-methyl-1*H*-pyrazolo[3,4-b]pyridine **5c** (450 mg, 2.23 mmol) and *N*-(piperidin-4-yl)tert-butyl carbamate (446 mg, 2.23 mmol) were dissolved in toluene (8 mL). $Pd_2(dba)_3$ (256 mg, 445 μmol), BINAP (554 mg, 890 μmol) and K_2CO_3 (615 mg, 4.45 mmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **13a** (78.0 mg, 213 μmol, yield: 9.57%) as yellow solid.
MS m/z (ESI): 366.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 6.95 (s, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.37 (d, J = 13.2 Hz, 2H), 3.85 (s, 3H), 3.53 (s, 1H), 3.02 (dd, J = 18.4, 6.8 Hz, 2H), 1.80 (d, J = 10.4 Hz, 2H), 1.39 (s, 9H), 1.35 (dd, J = 7.6, 4.4 Hz, 2H).

Step 2

N-[1-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-6-yl)piperidin-4-yl]tert-butyl carbamate **13b**

Compound **13a** (73.0 mg, 199 μmol) and Compound **4c** (133 mg, 199 μmol) were dissolved in dioxane (7.3 mL) and water (1.5 mL). Xphos-Pd-G2 (15.7 mg, 19.9 μmol), Xphos (19.0 mg, 39.9 μmol) and Cs_2CO_3 (130 mg, 399 μmol) were added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The residues were diluted with water (20 mL), and extracted with ethyl acetate (20.0 mL×3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the high-performance liquid chromatography (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 55%-65%), to obtain the title product **13b** (20.0 mg, 37.1 μmol, yield: 18.6%).
MS m/z (ESI): 539.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 2H), 7.45 – 7.31 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 4.4 Hz, 1H), 4.39 – 4.21 (m, 2H), 3.87 (d, J = 2.8 Hz, 3H), 3.52 (s, 1H), 3.40 – 3.34 (m, 2H), 3.01 (dd, J = 23.6, 11.6 Hz, 2H), 2.89 (dd, J = 13.6, 7.2 Hz, 1H), 1.81 (d, J = 11.2 Hz, 2H), 1.39 (s, 11H), 0.77 (s, 7H), 0.26 (d, J = 6.8 Hz, 2H).

Step 3

2-[6-(4-aminopiperidin-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl]-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **13c**

Compound **13b** (15.0 mg, 27.8 μmol) was dissolved in methane dioxide (0.3 mL), followed by the addition of

trifluoroacetic acid (0.1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **13c** (12 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 439.2 [M+1]

Step 4

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-4-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **13**

The crude product of Compound **13c** (12.0 mg, 37.3 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of Compound **3e** (6.68 mg, 27.3 μmol), and the mixture was stirred at room temperature for 1.5 hours. The mixture was cooled to 0°C, sodium triacetoxyborohydride (29.0 mg, 136 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **13** (12.0 mg, 18 μmol, yield: 65.7%) as white solid.
MS m/z (ESI): 667.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 8.0 Hz, 2H), 7.66 (dd, J = 12.4, 4.4 Hz, 2H), 7.59 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.38 (ddd, J = 19.2, 10.0, 4.0 Hz, 2H), 6.70 (d, J = 6.0 Hz, 1H), 4.26 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.87 (d, J = 3.2 Hz, 3H), 3.83 (s, 2H), 3.03 (d, J = 9.2 Hz, 2H), 2.89 (dd, J = 13.2, 6.8 Hz, 1H), 2.70 (s, 1H), 1.94 (d, J = 11.6 Hz, 2H), 1.30 (d, J = 9.6 Hz, 2H), 1.11 – 0.63 (m, 7H), 0.26 (d, J = 6.8 Hz, 2H).

Example 14

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]benzamide **14**

Step 1

3-{4-chloro-1*H*-pyrazolo[3,4-b]pyridin-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **14b**

4,6-Dichloro-1*H*-pyrazolo[3,4-b]pyridine **14a** (2.0 g, 10.64 mmol) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (3.14 g, 10.64 mmol) were dissolved in dioxane (30 mL) and water (5 mL). Sodium carbonate (3.38 g, 31.9 mmol) and Pd (dppf)Cl_2.DCM (779 mg, 1.06 mmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (40 mL) was added, and the mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **14b** (600 mg, 1.87 mmol, yield: 17.6%).
MS m/z (ESI): 321.1 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.43 – 7.28 (m, 1H), 6.94 – 6.74 (m, 1H), 4.65 (br s, 2H), 4.45 (br d, J = 12.9 Hz, 2H), 1.54 (br s, 9H).

Step 2

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1*H*-pyrazolo[3,4-b]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **14c**

Compound 1**4b** (600 mg, 1.87 mmol) and Compound **4c** (800 mg, 2.39 mmol) were dissolved in dioxane (8.0 mL) and water (1.5 mL). Cesium carbonate (1.83 g, 1.93 mmol) and Pd(dppf)Cl_2.DCM (122 mg, 187.2 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column

chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **14c** (170 mg, 344.4 μmol, yield: 18.4%) as brown solid.
MS m/z (ESI): 494.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.92 – 13.69 (m, 1H), 8.04 – 7.91 (m, 1H), 7.73 (dd, *J* = 5.5, 8.5 Hz, 1H), 7.55 – 7.35 (m, 3H), 6.69 (br d, *J* = 12.4 Hz, 1H), 4.61 – 4.46 (m, 2H), 4.29 (br d, *J* = 3.4 Hz, 2H), 3.41 – 3.32 (m, 2H), 2.79 (br dd, *J* = 6.7, 13.6 Hz, 1H), 1.46 (d, *J* = 7.3 Hz, 9H), 0.93 – 0.54 (m, 7H), 0.16 (br t, *J* = 6.0 Hz, 2H)

Step 3

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1*H*-pyrazolo[3,4-b]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **14d**

Compound **14c** (100 mg, 202.6 μmol) was dissolved in methanol (5.0 mL), followed by the addition of Pd/C (21.6 mg, 202.6 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **14d** (100 mg, 201.8 μmol, yield: 99.6%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 496.1 [M+1]

Step 4

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]benzamide **14e**

Compound **14d** (100 mg, 201.8 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **14e** (100 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 396.3 [M+1]

Step 5

N-[(1r,4r)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1*H*-pyrazolo[3,4-b]pyridin-6-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **14f**

The crude product of Compound **14e** (100 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (49.07 mg, 215.90 μmol) and triethylamine (59.58 mg, 588.82 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (37.00 mg, 588.82 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with a saturated aqueous sodium bicarbonate solution (10 mL), and extracted with dichloromethane (20 mL × 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% NH_4HCO_3), elution gradient: 40%-70%), to obtain the title Compound **14f** (70 mg, 115.36 μmol, yield: 58.8%) as white solid.
MS m/z (ESI): 607.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.68 – 13.51 (m, 1H), 7.93 (s, 1H), 7.74 – 7.63 (m, 1H), 7.51 – 7.31 (m, 2H), 7.08 (s, 1H), 6.67 (br d, *J* = 8.0 Hz, 1H), 3.60 – 3.46 (m, 1H), 3.22 – 3.06 (m, 1H), 2.98 (br t, *J* = 8.1 Hz, 1H), 2.89 – 2.72 (m, 2H), 2.56 (br d, *J* = 8.3 Hz, 1H), 2.32 – 2.01 (m, 4H), 1.89 – 1.67 (m, 4H), 1.36 (s, 9H), 1.17 – 1.03 (m, 2H), 0.94 – 0.84 (m, 4H), 0.79 – 0.61 (m, 4H), 0.19 (br dd, *J* = 4.4, 6.0 Hz, 2H)

Step 6

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]benzamide **14g**

Compound **14f** (60 mg, 98.88 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **14g** (65 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 507.4 [M+1]

Step 7

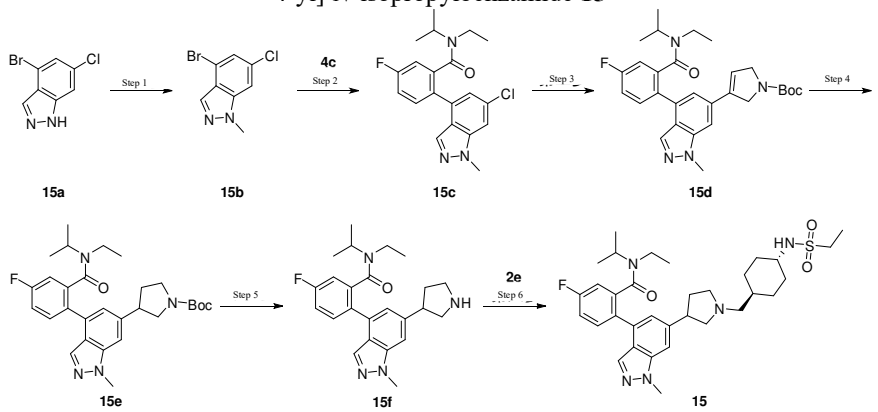
N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[3,4-b]pyridin-4-yl]benzamide **14**

The crude product of Compound **14g** (62 mg) was dissolved in dichloromethane (3.0 mL), followed by the addition of ethanesulfonyl chloride (26 mg, 202.2 μmol) and triethylamine (51 mg, 504 μmol), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% NH_4HCO_3), elution gradient: 34%-64%), to obtain the title Compound **14** (4.86 mg, 8.12 μmol, yield: 8.13 %) as white solid.
MS m/z (ESI): 599.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 7.93 (s, 1H), 7.72 – 7.64 (m, 1H), 7.47 – 7.33 (m, 2H), 7.08 (s, 1H), 7.04 – 6.92 (m, 1H), 3.58 – 3.47 (m, 2H), 3.03 – 2.91 (m, 4H), 2.89 – 2.81 (m, 1H), 2.78 – 2.71 (m, 1H), 2.60 – 2.54

(m, 1H), 2.30 – 2.16 (m, 3H), 2.13 – 2.02 (m, 1H), 1.91 – 1.72 (m, 4H), 1.43 – 1.13 (m, 7H), 1.09 – 0.81 (m, 6H), 0.81 – 0.59 (m, 4H), 0.25 – 0.13 (m, 2H).

Example 15

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-isopropylbenzamide **15**



Step 1

4-bromo-6-chloro-1-methyl-1*H*-indazole **15b**

4-Bromo-6-chloro-1*H*-indazole **15a** (2.0 g, 8.64 mmol) and cesium carbonate (5.63 g, 17.2 mmol) were dissolved in *N,N*-dimethylformamide (20 mL), followed by the addition of iodomethane (1.35 g, 9.50 mmol). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **15b** (1.30 g, 5.30 mmol, yield: 61.2%) as white solid.

MS m/z (ESI): 244.95 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 0.8 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.44 (d, J = 1.6 Hz, 1H), 4.06 (s, 3H).

Step 2

2-(6-chloro-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **15c**

Compound 1**5b** (500 mg, 2.04 mmol) and Compound **4c** (1.50 g, 2.24 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). Sodium carbonate (431 mg, 4.07 mmol) and Pd(dppf)Cl_2 (149 mg, 203 μmol) were added, and the mixture was stirred at 70 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **15c** (519 mg, 1.39 mmol, yield: 68.1%) as white solid.

MS m/z (ESI): 374.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.87 (m, 2H), 7.66 (dd, J = 8.4, 5.6 Hz, 1H), 7.45 – 7.32 (m, 2H), 7.07 (d, J = 1.6 Hz, 1H), 4.18 (dd, J = 13.6, 6.8 Hz, 0.18H), 4.06 (d, J = 1.6 Hz, 3H), 3.37 (s, 2H), 2.81 (dq, J = 13.6, 6.8 Hz, 0.89H), 1.07 (s, 7H), 0.17 (d, J = 6.8 Hz, 2H).

Step 3

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **15d**

Compound **15c** (886 mg, 1.42 mmol, 60% purity) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (419 mg, 1.42 mmol) were dissolved in dioxane (20 mL) and water (4 mL). Sodium carbonate (301 mg, 2.84 mmol) and Pd (dppf)Cl_2 (104 mg, 142 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. Water (50 mL) was added to the residues, and the mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **15d** (260 mg, 513 μmol, yield: 36.0%) as white solid.

MS m/z (ESI): 507.2 [M+1]

Step 4

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate

15e

Compound **15d** (260 mg, 513 μmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (26 mg). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **15e** (235 mg, 462 μmol, yield: 90%) as white solid.

MS m/z (ESI): 509.2 [M+1]

Step 5

N-ethyl-5-fluoro-2-[1-methyl-6-(pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **15f**

Compound **15e** (30 mg, 58.9 μmol) was dissolved in methane dioxide (0.9 mL), followed by the addition of trifluoroacetic acid (0.3 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **15f** (24 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.3 [M+1]

Step 6

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-isopropylbenzamide **15**

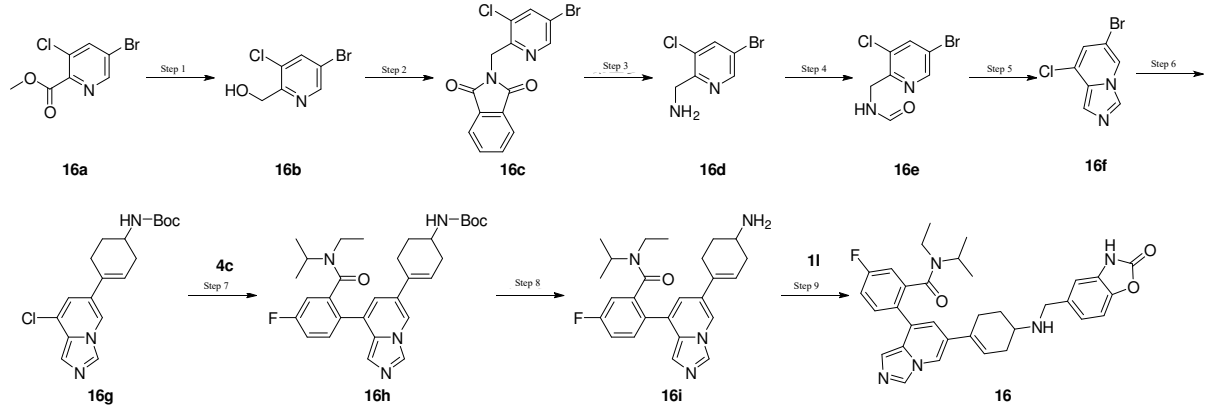
The crude product of Compound **15f** (24 mg) was dissolved in *N,N*-dimethylformamide (1.0 mL), followed by the addition of potassium carbonate (24.3 mg, 176 μmol), and the mixture was stirred at room temperature for 0.5 hours. Potassium iodide (9.75 mg, 58.7 μmol) and Compound **2e** (55.5 mg, 117μmol) were added, and the mixture was stirred at 80°C to allow for reacting for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **15** (7.0 mg, 11.4 μmol, yield: 19.4 %) as white solid.

MS m/z (ESI): 612.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.57 (dt, *J* = 10.0, 5.2 Hz, 1H), 7.52 (s, 1H), 7.38 (t, *J* = 8.8 Hz, 1H), 7.30 (s, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 4.25 – 4.16 (m, 0.3H), 4.02 (d, *J* = 3.2 Hz, 3H), 3.39 (d, *J* = 6.8 Hz, 2H), 3.25 (d, *J* = 6.8 Hz, 1H), 2.96 (dd, *J* = 7.2, 3.2 Hz, 2H), 2.86 (ddd, *J* = 20.4, 13.6, 7.8 Hz, 3H), 2.71 – 2.59 (m, 2H), 2.45 (d, *J* = 8.8 Hz, 1H), 2.24 (d, *J* = 6.8 Hz, 3H), 1.94 – 1.75 (m, 5H), 1.10 (ddd, *J* = 128, 66.4, 4.4 Hz, 12H), 0.67 (t, *J* = 6.8 Hz, 3H), 0.13 – 0.06 (m, 2H).

Example 16

N-ethyl-5-fluoro-2-[6-(4-{[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]amino}cyclohexyl-1-ene-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-isopropylbenzamide **16**



Step 1

(5-bromo-3-chloropyridin-2-yl)methanol **16b**

5-Bromo-3-chloropyridin-2-methyl carboxylate **16a**(25 g, 99.8 mmol) was dissolved in methanol (250 mL) and tetrahydrofuran (250 mL), cooled to 0°C, followed by the addition of sodium borohydride (20 g, 528.7 mmol). The mixture was stirred at room temperature to allow for reacting for 8.0 hour. The reaction mixture was cooled to 0°C, quenched by adding water (40 mL), and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **16b** (18 g, 80.9 mmol, yield: 81.1%) as white solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 223.8 [M+1]

Step 2

2-[(5-bromo-3-chloropyridin-2-yl)methyl]-2,3-dihydro-1*H*-isoindol-1,3-dione **16c**

Compound **16b** (13 g, 58.4 mmol), 2,3-dihydro-1*H*-isoindol-1,3-dione (9.5 g, 64.6 mmol) and triphenylphosphine (23 g, 87.69 mmol) were dissolved in tetrahydrofuran (100 mL), and cooled to 0°C under a nitrogen atmosphere, followed by the addition of DIAD (17.7 g, 87.53 mmol). The mixture was stirred at room temperature to allow for reacting for 12 hours, with white solid precipitated. The reaction mixture was filtered under a reduced pressure, and the filter cake was washed with ethyl acetate and then dried under a reduced pressure, to obtain the crude product of title Compound **16c** (14 g, 39.8 mmol, yield: 68.1%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 352.8 [M+1]

Step 3

(5-bromo-3-chloropyridin-2-yl)methylamine **16d**

Compound **16c** (19.3 g, 54.9 mmol) was dissolved in the solution of methylamine in ethanol (170.49 g, 1.65 mol, 189.64 mL, 30% purity). The mixture was stirred at 65°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature and concentrated under a reduced pressure, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **16d** (30 g, 135 mmol, yield: 247%) was obtained as blue solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 222.9 [M+1]

Step 4

N-[(5-bromo-3-chloropyridin-2-yl)methyl]formamide **16e**

Compound **16d** (6.0 g, 27.1 mmol) was dissolved in ethyl formate (60 mL), followed by the addition of triethylamine (4.36 g, 43.1 mmol). The mixture was stirred at 70°C to allow for reacting for 12 hours. The reaction mixture was cooled under reduced pressure to room temperature, and concentrated under a reduced pressure, to obtain the crude product of title Compound **16e** (6.0 g, 24.05 mmol, yield: 88.8%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 251.0 [M+1]

Step 5

6-bromo-8-chloroimidazo[1,5-a]pyridine **16f**

Compound **16e**(24.0 g, 96.2 mmol) was dissolved in toluene (200 mL), followed by the addition of phosphorus oxychloride (73.75 g, 480.98 mmol). The mixture was stirred at 100°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The residues were dissolved in dichloromethane (40 mL), followed by the addition of an aqueous sodium hydroxide solution (3 M, 60 mL). The mixture was extracted with dichloromethane (100 mL x 3), and the organic phases were combined, dried over anhydrous sodium sulfate, concentrated under a reduced pressure . The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **16f** (4.0 g, 17.28 mmol, yield: 17.96%) as yellow oil.

MS m/z (ESI): 233.0 [M+1]

Step 6

N-(4-{8-chloroimidazo[1,5-a]pyridin-6-yl}cyclohexyl-3-ene-1-yl)tert-butyl carbamate **16g**

Compound **16f** (760 mg, 3.28 mmol), *N*-[4-(tetramethyl-1,3,2-dioxaboran-2-yl)cyclohexyl-3-ene-1-yl]tert-butyl carbamate (950 mg, 2.94 mmol) and sodium carbonate (1.04 g, 9.85 mmol) were dissolved in dioxane (15 mL) and water (1.5 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2.DCM (270 mg, 330 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 8.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **16g** (750 mg, 2.16 mmol, yield: 65.67%).

MS m/z (ESI): 348.0 [M+1]

Step 7

N-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-6-yl}cyclohexyl-3-ene-1-yl)tert-butyl carbamate **16h**

Compound **16g** (750 mg, 2.16 mmol), Compound **4c** (1.08 g, 3.23 mmol) and cesium carbonate (2.11 g, 6.47 mmol) were dissolved in dioxane (10 mL) and water (1.0 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (140.5 mg, 215.6 μmol) was added, and the mixture was stirred at 100°C to allow for reacting for 8.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (40 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using

petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **16h** (730 mg, 1.40 mmol, yield: 65.0%).
MS m/z (ESI): 521.2 [M+1]

Step 8

2-[6-(4-aminocyclohex-1-ene-1-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **16i**

Compound **16h** (90 mg, 172.9 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (197.10 mg, 1.73 mmol, 133.18 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **16i** (70 mg, 166.46 μmol, 96.29% yield). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 421.2 [M+1]

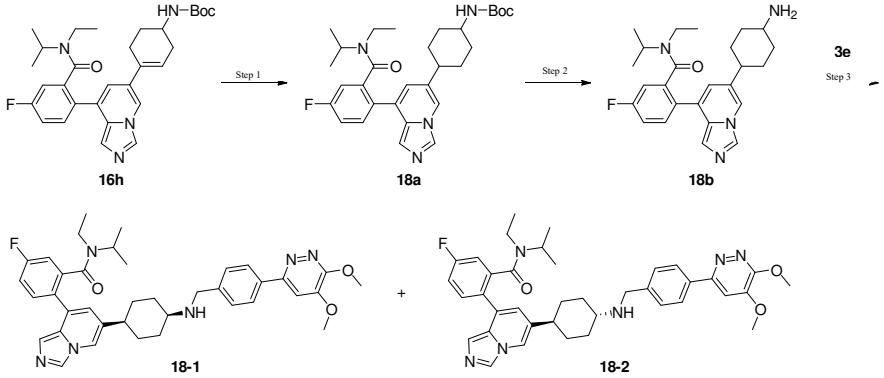
Step 9

N-ethyl-5-fluoro-2-[6-(4-{[(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)methyl]amino}cyclohexyl-1-ene-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-isopropylbenzamide **16**

Compound **16i** (50 mg, 93.54 μmol, trifluoroacetate) was dissolved in dichloromethane (2.0 mL), followed by the addition of triethylamine (94.65 mg, 935.38 μmol) and Compound **1l** (30.52 mg, 187.08 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (25 mg, 397.82 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for 12 hours. An aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 8%-38%), to obtain the title Compound **16** (22.2 mg, 39.1 μmol, yield: 41.8%)
MS m/z (ESI): 568.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 – 8.24 (m, 3H), 7.73 (dd, J = 5.2, 8.4 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.29 – 7.22 (m, 4H), 7.03 (s, 1H), 6.20 (s, 1H), 4.28 – 4.14 (m, 2H), 3.61 – 3.33 (m, 2H), 3.04 – 2.90 (m, 1H), 2.84 – 2.23 (m, 6H), 1.93 – 1.70 (m, 1H), 1.36 – 0.73 (m, 7H), 0.29 (d, J = 6.4 Hz, 2H).

Examples 18-1 and 18-2

N-ethyl-5-fluoro-*N*-(isopropyl)-2-{6-[(1*s*,4*s*)-4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **18-1**
N-ethyl-5-fluoro-*N*-(isopropyl)-2-{6-[(1*r*,4*r*)-4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **18-2**



Step 1

N-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)cyclohexyl]tert-butyl carbamate **18a**

Compound **16h** (300 mg, 576.2 μmol) was dissolved in methanol (25 mL), followed by the addition of Pd/C (250 mg, 2.06 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The residues were dissolved in methanol (25 mL), followed by the addition of Pd/C (250 mg, 2.06 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was further stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:40%-70%), to obtain the title Compound **18a** (170 mg, 325.3 μmol, yield: 56.5%) as yellow solid.
MS m/z (ESI): 523.2 [M+1]

Step 2

2-[6-(4-aminocyclohexyl)imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **18b**

Compound **18a**(170 mg, 325.3 μmol) was dissolved in methane dioxide (10 mL), followed by the addition of trifluoroacetic acid (370.88 mg, 3.25 mmol, 250.99 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **18b** (130 mg, 307.67 μmol, 94.59% yield). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 423.2 [M+1]

Step 3

N-ethyl-5-fluoro-*N*-(isopropyl)-2-{6-[(1*s*,4*s*)-4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **18-1**
N-ethyl-5-fluoro-*N*-(isopropyl)-2-{6-[(1*r*,4*r*)-4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)cyclohexyl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **18-2**

Compound **18b** (200 mg, 372.74 μmol, trifluoroacetate) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (113.15 mg, 1.12 mmol) and Compound **3e**(72.83 mg, 298.20 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (70.27 mg, 1.12 mmol) was added, and the mixture was stirred at 45°C to allow for reacting for 12 hours. An aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:43%-73%), to obtain the title Compounds **18-1** (12.46 mg, 19.15 μmol, yield: 5.14%) and **18-2** (19.67 mg, 30.23 μmol, yield: 8.11%)

Single-configuration Compound 18-1:
MS m/z (ESI):651.1 [M+1]
HPLC analysis: retention time: 1.307 min, 10-80AB_4min.lcm
SFC analysis: retention time: 1.604 min; chromatographic column: Cellulose-2 50×4.6 mm I.D., 3 um; mobile phase: CO2/[MeOH+ACN (0.05% DEA)] = 40/60.
1H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.17 (s, 1H), 8.03 (d, J=8.0 Hz, 2H), 7.67 (dd, J=6.0, 8.4 Hz, 1H), 7.59 (s, 1H), 7.49 (d, J=7.6 Hz, 2H), 7.40 – 7.27 (m, 2H), 7.10 (s, 1H), 6.63 – 6.58 (m, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.83 (s, 2H), 3.47 – 3.38 (m, 1H), 3.30 – 3.22 (m, 1H), 3.00 – 2.83 (m, 1H), 2.47 – 2.33 (m, 2H), 2.17 – 1.96 (m, 3H), 1.83 (d, J=12.0 Hz, 2H), 1.47 – 1.32 (m, 2H), 1.26 – 1.13 (m, 2H), 1.08 – 0.84 (m, 4H), 0.80 – 0.69 (m, 3H), 0.24 (d, J=6.4 Hz, 2H).

Single-configuration Compound 18-2:
MS m/z (ESI):651.2 [M+1]
HPLC analysis: retention time: 1.379 min, 10-80AB_4min.lcm
SFC analysis: retention time: 0.911 min; chromatographic column: Cellulose-2 50×4.6 mm I.D., 3 um; mobile phase: CO2/[MeOH+ACN (0.05% DEA)] = 40/60.
^{1}H NMR (400 MHz, DMSO-d_6) δ8.36 (s, 1H), 8.20 (s, 1H), 8.03 (d, J=8.0 Hz, 2H), 7.68 (dd, J=5.6, 8.4 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J=8.0 Hz, 2H), 7.41 – 7.27 (m, 2H), 7.10 (s, 1H), 6.69 – 6.63 (m, 1H), 4.05 (s, 3H), 3.98 (s, 3H), 3.77 (s, 2H), 3.43 (td, J=6.4, 13.2 Hz, 1H), 3.30 – 3.25 (m, 1H), 2.96 – 2.76 (m, 2H), 2.47 – 2.37 (m, 1H), 2.21 – 2.07 (m, 1H), 1.95 – 1.77 (m, 4H), 1.54 (d, J=11.6 Hz, 4H), 0.94 – 0.68 (m, 7H), 0.26 (d, J=6.4 Hz, 2H).

Example 19

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]imidazo[1,5-*a*]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **19**

Step 1

N-(1-{8-chloroimidazo[1,5-*a*]pyridin-6-yl}piperidin-4-yl)tert-butyl carbamate **19a**

Compound **16f** (1.0 g, 4.32 mmol), *N*-(piperidin-4-yl)tert-butyl carbamate (870 mg, 4.34 mmol) and cesium carbonate (4.22 g, 12.96 mmol) were dissolved in dioxane (15 mL). Ruphos (202 mg, 432.9 μmol) and Pd_2 (dba)$_3$ (400 mg, 436.38 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (35 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **19a**

(315 mg, 897.8 μmol, yield: 20.78%).
MS m/z (ESI): 351.1 [M+1]

Step 2

N-[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)piperidin-4-yl]tert-butyl carbamate **19b**

Compound **19a** (315 mg, 897.8 μmol) and Compound **4c** (362 mg, 1.08 mmol) were dissolved in dioxane (4 mL) and water (0.8 mL). Potassium phosphate (572 mg, 2.69 mmol) and $Pd(dtbpf)Cl_2$ (59 mg, 90.5 μmol) were added, and the mixture was stirred at 80 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (25 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **19b** (300 mg, 572.9 μmol, yield: 63.8%).
MS m/z (ESI): 524.3 [M+1]

Step 3

2-[6-(4-aminopiperidin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **19c**

Compound **19b** (300 mg, 572.9 μmol) was dissolved in methane dioxide (5 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **19c** (300 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 424.2 [M+1]

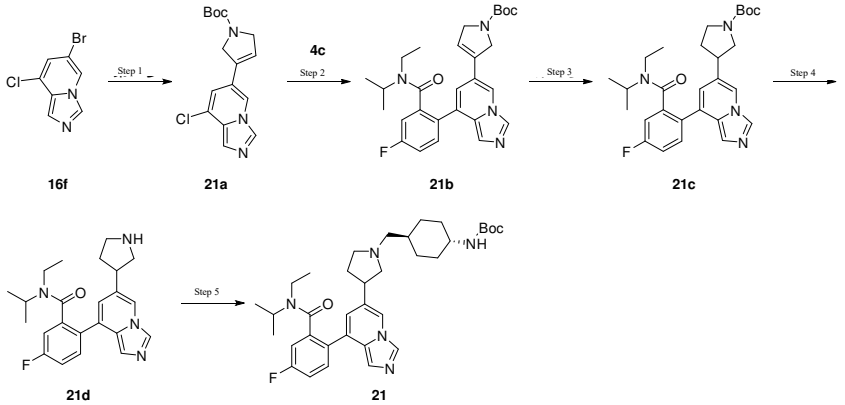
Step 4

2-{6-[4-({[4-(5,6-dimethoxypyridazin-3-yl)phenyl]methyl}amino)piperidin-1-yl]imidazo[1,5-*a*]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **19**

The crude product of Compound **19c** (150 mg, 279 μmol, trifluoroacetate), Compound **3e**(69 mg, 282.5 μmol) and triethylamine (57 mg, 563 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (53 mg, 843.4 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 30%-60%), to obtain the title Compound **19** (13.12 mg, 20.13 μmol, yield: 7.21%) as white solid.
MS m/z (ESI): 652.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.10 – 7.97 (m, 2H), 7.78 (s, 1H), 7.72 – 7.64 (m, 1H), 7.59 (s, 1H), 7.54 – 7.45 (m, 2H), 7.42 – 7.27 (m, 2H), 7.08 – 7.01 (m, 1H), 6.69 – 6.59 (m, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.85 (s, 2H), 3.50 – 3.39 (m, 3H), 2.99 – 2.86 (m, 1H), 2.84 – 2.54 (m, 4H), 2.02 – 1.88 (m, 2H), 1.52 – 1.37 (m, 2H), 0.96 – 0.70 (m, 7H), 0.34 – 0.28 (m, 2H).

Example 21

N-[(1r,4r)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **21**



Step 1

3-{8-chloroimidazo[1,5-*a*]pyridin-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **21a**

Compound **16f** (2.0 g, 6.91 mmol), 3-(tetramethyl-1, 3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (1.8 g, 6.10 mmol) and sodium carbonate (2.18 g, 20.6 mmol) were dissolved in dioxane (30 mL) and water

(3 mL). Pd (dppf)Cl_2.DCM (282.24 mg, 345.6 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **21a** (1.2 g, 3.75 mmol, yield: 54.29%).
MS m/z (ESI): 320.1 [M+1]

Step 2

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **21b**

Compound **21a** (1.2 g, 3.75 mmol) and Compound **4c** (2.62 g, 7.81 mmol) were dissolved in dioxane (24 mL) and water (2.5 mL). Cesium carbonate (3.67 g, 11.26 mmol) and Pd(dtbpf)Cl_2 (244.57 mg, 375.2 μmol) were added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 8.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **21b** (1.43 g, 2.9 mmol, yield: 77.4%).
MS m/z (ESI): 493.2 [M+1]

Step 3

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **21c**

Compound **21b** (430 mg, 873 μmol) was dissolved in methanol (20 mL), followed by the addition of Pd/C (103.4 mg, 873 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **21c** (400 mg, 808.7 μmol, yield: 92.6%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 495.3 [M+1]

Step 4

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]benzamide **21d**

Compound **21c** (400 mg, 808.7 μmol) was dissolved in dichloromethane (10 mL), followed by the addition of trifluoroacetic acid (922.14 mg, 8.09 mmol, 623.07 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **21d** (300 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 395.3 [M+1]

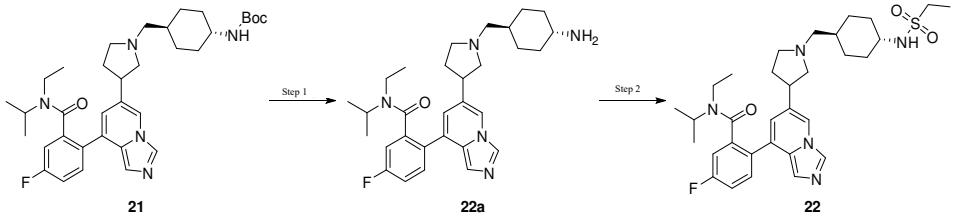
Step 5

N-[(1*r*,4*r*)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **21**

The crude product of Compound **21d** (300 mg, 590 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (201.15 mg, 884.94 μmol) and triethylamine (298.49 mg, 2.95 mmol) were dissolved in methanol (10 mL), and stirred at room temperature for 0.5 hours.Sodium cyanoborohydride (74.15 mg, 1.18 mmol) was added, and the reaction mixture was stirred at room temperature for 1.0 hour. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 58%-78%), to obtain the title Compound **21** (142 mg, 234.4 μmol, yield: 39.1%) as white solid.
MS m/z (ESI): 606.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 – 8.32 (m, 1H), 8.23 – 8.19 (m, 1H), 7.69 – 7.62 (m, 1H), 7.40 – 7.27 (m, 2H), 7.10 (s, 1H), 6.71 – 6.63 (m, 2H), 3.49 – 3.38 (m, 1H), 3.29 – 3.06 (m, 3H), 2.99 – 2.77 (m, 2H), 2.68 – 2.54 (m, 2H), 2.47 – 2.32 (m, 1H), 2.29 – 2.10 (m, 3H), 1.87 – 1.65 (m, 5H), 1.39 – 1.34 (m, 9H), 1.33 – 1.25 (m, 1H), 1.18 – 1.00 (m, 3H), 0.94 – 0.81 (m, 5H), 0.79 – 0.71 (m, 3H), 0.28 (dd, *J* = 6.8, 12.4 Hz, 2H).

Example 22

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]benzamide **22**



Step 1

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]benzamide **22a**

Compound **21** (100 mg, 165.08 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **22a** (80 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 506.5 [M+1]

Step 2

N-ethyl-5-fluoro-*N*-isopropyl-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]benzamide **22**

The crude product of Compound **22a** (80 mg) was dissolved in dichloromethane (3.0 mL), followed by the addition of ethanesulfonyl chloride (40.7 mg, 316.4 μmol) and triethylamine (80.04 mg, 791 μmol), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with dichloromethane (20 mL), followed by the addition of a saturated aqueous sodium carbonate solution (20 mL). The mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%), to obtain the title Compound **22** (1.92 mg, 3.21 μmol, yield: 2.03 %) as white solid.

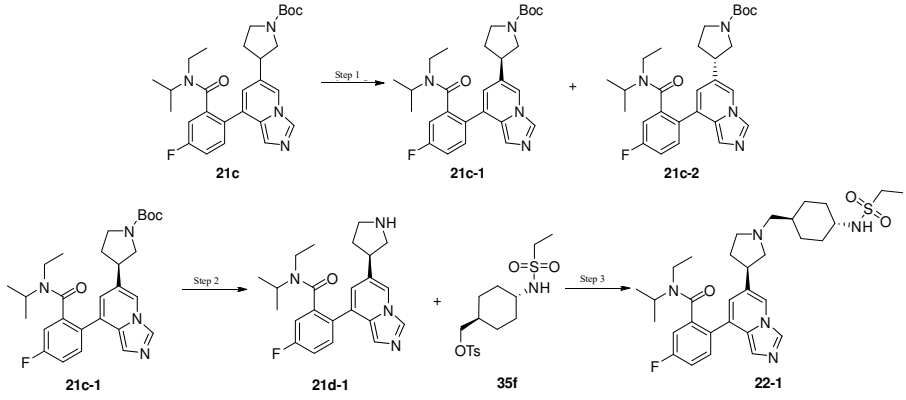
MS m/z (ESI): 598.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.57 – 8.16 (m, 3H), 7.71 (dd, *J* = 5.2, 8.4 Hz, 1H), 7.35 (dt, *J* = 2.8, 8.4 Hz, 1H), 7.29 – 7.21 (m, 2H), 6.86 – 6.80 (m, 1H), 3.56 (td, *J* = 6.4, 12.0 Hz, 1H), 3.45 – 3.38 (m, 2H), 3.20 – 2.91 (m, 5H), 2.81 – 2.58 (m, 3H), 2.43 – 2.30 (m, 1H), 2.03 (d, *J* = 4.8 Hz, 3H), 1.96 – 1.87 (m, 2H), 1.56 (s, 1H), 1.38 – 1.25 (m, 6H), 1.18 – 1.03 (m, 3H), 1.01 – 0.88 (m, 6H), 0.82 (t, *J* = 7.2 Hz, 1H), 0.32 (dd, *J* = 4.4, 6.4 Hz, 2H).

Examples 22-1 and 22-2

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*R*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **22-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*S*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **22-2**



Step 1

(3*R*)-3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **21c-1**

(3*S*)-3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **21c-2**

Compound **21c** (1.38 g, 2.78 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK OD (250 mm * 30 mm,10 um), mobile phase: 35%-35% (v/v) carbon dioxide-ethanol (0.1% ammonia water)), to obtain the title Compounds **21c-1** (490 mg, 990.7 μmol, yield: 35.5%) and **21c-2** (524 mg, 1.06 mmol, yield: 38.0%).

Single-configuration Compound 21c-1:

MS m/z (ESI):495.6 [M+1]

SFC analysis: retention time: 1.42 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: 5%-40% (v/v) EtOH (0.05% DEA)/CO_2.

Single-configuration Compound 21c-2:

MS m/z (ESI):495.4 [M+1]

SFC analysis: retention time: 0.817 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: 5%-40% (v/v) EtOH (0.05% DEA)/CO_2.

Steps 2 and 4

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*R*)-pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-8-yl]benzamide **21d-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*S*)-pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-8-yl]benzamide **21d-2**

Compound **21c-1/21c-2** (220 mg/150 mg, 244.8 μmol/303.3 μmol) was dissolved in methane dioxide (4.5 mL/3.0 mL), followed by the addition of trifluoroacetic acid (1.5 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0/0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **21d-1/21d-2** (168 mg/155 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 21d-1:

MS m/z (ESI): 395.3 [M+1]

Single-configuration Compound 21d-2:

MS m/z (ESI): 395.1 [M+1]

Steps 3 and 5

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*R*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-8-yl}benzamide **22-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{6-[(3*S*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **22-2**

The crude product of Compound **21c-1/21c-2** (160 mg/154 mg) was dissolved in DMF (3.0 mL/3.0 mL), followed by the addition of potassium carbonate (217 mg/209 mg, 1.57 mmol/1.52 mmol), TBAI(11.6 mg/11.2 mg, 31.5 μmol/30.3 μmol) and Compound **35f**(142 mg/228 mg, 378 μmol/606 μmol), and the mixture was stirred at 90°C for (12.0/12.0) hours. An aqueous sodium bicarbonate solution (10 mL/10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3/20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water)/acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 34%-64%/24%-54%), to obtain the title Compound **22-1/22-2** (7.68 mg/15.58 mg, 12.85 μmol/26.06 μmol, yield: 4.08%/8.60%)

Single-configuration Compound 22-1:

MS m/z (ESI):598.2 [M+1]

Chiral HPLC: retention time: 1.653 min; chromatographic column: Chiralcel OD-3 50 X 4.6 mm I.D., 3 um; mobile phase: 5%-40% (v/v) MeOH (0.05% DEA)/CO_2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.24 – 8.18 (m, 1H), 7.70 – 7.62 (m, 1H), 7.41 – 7.26 (m, 2H), 7.10 (s, 1H), 7.01 – 6.96 (m, 1H), 6.72 – 6.64 (m, 1H), 3.51 – 3.37 (m, 1H), 3.24 – 3.18 (m, 1H), 3.02 – 2.90 (m, 4H), 2.85 – 2.76 (m, 1H), 2.64 – 2.53 (m, 2H), 2.47 – 2.32 (m, 1H), 2.29 – 2.12 (m, 3H), 1.88 – 1.73 (m, 5H), 1.39 – 1.13 (m, 7H), 0.97 – 0.71 (m, 9H), 0.31 – 0.24 (m, 2H).

Single-configuration Compound 22-2:

MS m/z (ESI):598.2 [M+1]

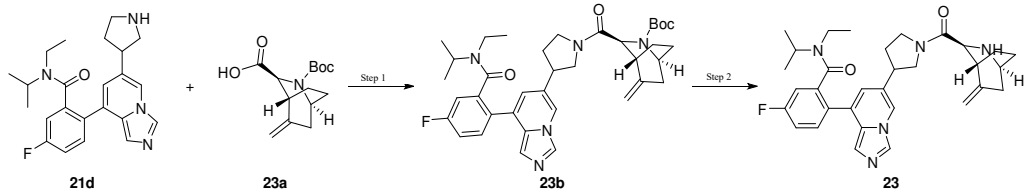
Chiral HPLC: retention time: 1.717 min; chromatographic column: Chiralcel OD-3 50 X 4.6 mm I.D., 3 um; mobile phase: 5%-40% (v/v) MeOH (0.05% DEA)/CO_2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (br d, J = 7.9 Hz, 1H), 8.28 – 8.18 (m, 1H), 7.74 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.16 – 7.08 (m, 1H), 6.68 – 6.57 (m, 1H), 8.35 (s, 1H), 8.26 – 8.16 (m, 1H), 7.74 – 7.59 (m, 1H), 7.45 –

7.25 (m, 2H), 7.20 – 6.82 (m, 2H), 6.73 – 6.63 (m, 1H), 3.48 – 3.39 (m, 1H), 3.24 – 3.18 (m, 1H), 3.06 – 2.87 (m, 4H), 2.86 – 2.76 (m, 1H), 2.69 – 2.54 (m, 2H), 2.48 – 2.36 (m, 1H), 2.33 – 2.11 (m, 3H), 1.89 – 1.73 (m, 4H), 1.64 – 1.48 (m, 1H), 1.39 – 1.12 (m, 7H), 0.97 – 0.72 (m, 9H), 0.32 – 0.23 (m, 2H).

Example 23

N-ethyl-5-fluoro-2-(6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]pyrrolidin-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **23**



21d **23a** **23b** **23**

Step 1

(1*S*,3*S*,4*R*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]- 4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-carbonyl]-5-methylene-2-azabicyclo[2. 2.2]octan-2-tert-butyl carboxylate **23b**

Compound **21d** (90.0 mg, 177 μmol, trifluoroacetate), (1*S*,3*S*,4*R*)-2-tert-butoxycarbonyl-5-methylene-2-azabicyclo[2.2.2]octan-3-carboxylic acid **23a** (45.0 mg, 265.5 μmol, prepared by referring to the method disclosed in Reference Example 13 on Page 93 in the Patent Application No. WO2020032105A1) and *N,N*-diisopropylethylamine (89.6 mg, 693 μmol) were dissolved in dichloromethane (3 mL), and cooled to 0°C. EDCI (50.89 mg, 265.48 μmol) and HOBt (40.66 mg, 265.48 μmol) were added, and the mixture was stirred at room temperature for 12 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 41%-71%), to obtain the title Compound **23b** (30 mg, 46.6 μmol, yield: 26.3%) as white solid.

MS m/z (ESI): 644.3 [M+1]

Step 2

N-ethyl-5-fluoro-2-(6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]pyrrolidin-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **23**

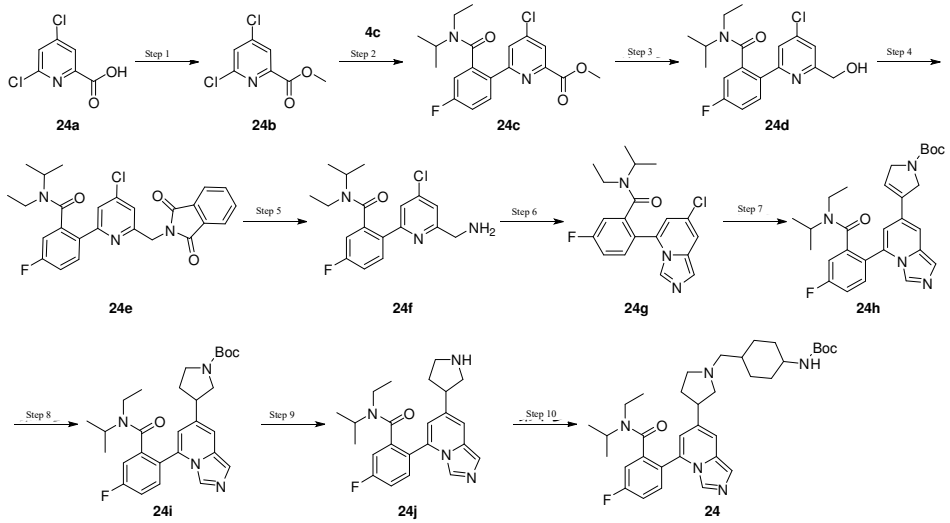
Compound **23b** (25.0 mg, 38.8 μmol) was dissolved in methane dioxide (4.8 mL) and trifluoroacetic acid (0.2 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compound **23** (8.84 mg, 16.26 μmol, yield: 41.87%).

MS m/z (ESI): 544.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.40 – 8.34 (m, 1H), 8.28 – 8.21 (m, 1H), 7.71 (dd, *J* = 5.2, 8.4 Hz, 1H), 7.40 – 7.31 (m, 1H), 7.29 – 7.20 (m, 2H), 6.87 – 6.77 (m, 1H), 5.11 – 4.95 (m, 1H), 4.14 – 3.75 (m, 3H), 3.69 – 3.47 (m, 3H), 3.46 – 3.35 (m, 2H), 3.17 – 3.12 (m, 1H), 3.10 – 2.94 (m, 1H), 2.77 – 2.53 (m, 3H), 2.33 – 1.99 (m, 2H), 1.96 – 1.70 (m, 2H), 1.65 – 1.51 (m, 2H), 1.17 – 1.05 (m, 1H), 0.97 (d, *J* = 5.6 Hz, 3H), 0.93 – 0.78 (m, 4H), 0.36 – 0.29 (m, 2H).

Example 24

N-[4-{[3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-7-yl}pyrrolidin-1-yl)methyl)cyclohexyl)tert-butyl carbamate **24**



Step 1

4,6-dichloropyridin-2-methyl carboxylate **24b**

4,6-Dichloropyridin-2-carboxylic acid **24a** (15 g, 78.13 mmol) was dissolved in methanol (150 mL), and cooled to 0°C, followed by the slow addition of $SOCl_2$ (18.59 g, 156.25 mmol). The mixture was stirred at 65°C to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, and dichloromethane (150 mL) was added to dissolve the residues. The organic phase was washed with saturated aqueous sodium bicarbonate solution (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **24b** (15 g, 72.8 mmol, yield: 93.2%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 206.0 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 4.00 (s, 3H).

Step 2

4-chloro-6-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyridin-2-methyl carboxylate **24c**

Compound **24b** (3.93 g, 19.09 mmol), Compound **4c** (6.4 g, 19.09 mmol) and sodium carbonate (6.07 g, 57.28 mmol) were dissolved in dioxane (35 mL) and water (5.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (1.40 g, 1.91 mmol) was added, and the mixture was stirred at 75°C to allow for reacting for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **24c** (6.0 g, 15.84 mmol, yield: 82.96%).

MS m/z (ESI): 379.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 – 8.04 (m, 1H), 7.95 – 7.90 (m, 1H), 7.88 – 7.81 (m, 1H), 7.46 – 7.39 (m, 1H), 7.32 – 7.26 (m, 1H), 3.90 – 3.88 (m, 3H), 3.57 (td, *J* = 6.6, 13.3 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.21 – 3.02 (m, 2H), 1.07 – 0.97 (m, 6H), 0.76 (br d, *J* = 6.5 Hz, 3H)**.**

Step 3

2-[4-chloro-6-(hydroxymethyl)pyridin-2-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **24d**

Compound **24c** (6.0 g, 15.84 mmol) was dissolved in tetrahydrofuran (60 mL) and methanol (60 mL). The reaction mixture was cooled to 0°C, followed by adding $NaBH_4$ (2.5 g, 66.1 mmol). The mixture was stirred at room temperature to allow for reacting for 8 hour. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **24d** (4.7 g, 13.4 mmol, yield: 84.6%) was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 351.0 [M+1]

Step 4

2-{4-chloro-6-[(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)methyl]pyridin-2-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **24e**

Compound **24d** (4.7 g, 13.4 mmol), 2,3-dihydro-1*H*-isoindol-1,3-dione (2.37 g, 16.1 mmol) and triphenylphosphine (4.22 g, 16.1 mmol) were dissolved in tetrahydrofuran (60 mL), and cooled to 0°C under a nitrogen atmosphere,

followed by the dropwise addition of DIAD(4.06 g, 20.1 mmol). The mixture was stirred at room temperature to allow for reacting for 12 hours, and the reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **24e** (3.5 g, 7.29 mmol, yield: 54.4%).
MS m/z (ESI): 480.2 [M+1]

Step 5

2-[6-(aminomethyl)-4-chloropyridin-2-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **24f**

Compound **24e** (3.5 g, 7.29 mmol) was dissolved in the solution of methylamine in ethanol ((45 g, 434.68 mmol, 50.06 mL, 30% purity). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The crude product of title Compound **24f** (3.5 g, 10.0 mmol, yield: 137.2 %) was obtained. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 350.1 [M+1]

Step 6

2-{7-chloroimidazo[1,5-a]pyridin-5-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **24g**

Compound **24f** (1.75 g, 5.0 mmol) was dissolved in ethyl formate (20 mL), followed by the addition of triethylamine (3.04 g, 30.1 mmol). The mixture was stirred at 70℃ to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature under a reduced pressure, and concentrated under a reduced pressure, and the obtained crude product (1.5 g, 5.03 mmol) was dissolved in toluene (15 mL), followed by the addition of phosphorus oxychloride (3.65 g, 23.82 mmol). The mixture was stirred at 100℃ to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The residues were dissolved in dichloromethane (20 mL), and a saturated aqueous sodium bicarbonate solution was added to regulate PH to 8. The mixture was extracted with dichloromethane (35 mL x 3), and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **24g** (810 mg, 2.25 mmol, yield: 56.7%).
MS m/z (ESI): 360.0 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 – 7.83 (m, 2H), 7.56 – 7.40 (m, 4H), 6.59 – 6.43 (m, 1H), 3.79 – 3.43 (m, 2H), 3.00 – 2.80 (m, 1H), 1.03 – 0.63 (m, 9H).

Step 7

3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **24h**

Compound **24g** (810 mg, 2.25 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (697.71 mg, 2.36 mmol) and potassium phosphate (1.19 g, 5.63 mmol) were dissolved in dioxane (10 mL) and water (1.5 mL). Pd (dppf)Cl_2 (150 mg, 230.15 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 80°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **24h** (780 mg, 1.58 mmol, yield: 70.34%).
MS m/z (ESI): 493.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 – 7.63 (m, 2H), 7.58 – 7.39 (m, 4H), 7.00 – 6.65 (m, 1H), 6.45 – 6.13 (m, 1H), 4.40 (br d, J = 3.0 Hz, 2H), 4.29 – 4.14 (m, 2H), 3.75 – 3.39 (m, 2H), 3.04 – 2.73 (m, 1H), 1.45 (d, *J* = 8.8 Hz, 9H), 1.03 – 0.38 (m, 9H).

Step 8

3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-tert-butyl formate **24i**

Compound **24h** (320 mg, 649.6 μmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (200 mg, 1.88 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **24i** (300 mg, 606.55 μmol, yield: 93.4%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 495.3 [M+1]

Step 9

N-ethyl-5-fluoro-*N*-isopropyl-2-[7-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]benzamide **24j**

Compound **24i** (387 mg, 782.45 μmol) was dissolved in methane dioxide (5.0 mL), followed by the addition of trifluoroacetic acid (3.70 g, 32.45 mmol, 2.5 mL) at 0°C. The mixture was stirred at room temperature to allow for

reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **24j** (400 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 395.2 [M+1]

Step 10

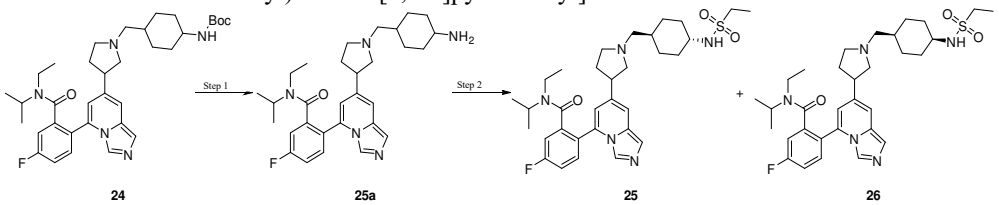
N-(4-{[3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-yl]methyl}cyclohexyl)tert-butyl carbamate **24**

The crude product of Compound **24j** (400 mg, 786.62 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (215 mg, 945.89 μmol) and triethylamine (160 mg, 1.58 mmol) were dissolved in methanol (5.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (150 mg, 2.39 mmol) was added, and the reaction mixture was stirred at room temperature for 11 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **24** (340 mg, 561.26 μmol, yield: 71.35%).
MS m/z (ESI): 606.6 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 – 7.64 (m, 2H), 7.50 – 7.27 (m, 4H), 6.74 – 6.61 (m, 1H), 6.57 – 6.45 (m, 1H), 3.64 – 3.41 (m, 1H), 3.28 – 3.20 (m, 1H), 3.19 – 3.06 (m, 1H), 2.97 – 2.73 (m, 2H), 2.67 – 2.54 (m, 2H), 2.47 – 2.31 (m, 1H), 2.29 – 2.09 (m, 3H), 1.97 – 1.60 (m, 5H), 1.57 – 0.51 (m, 24H).

Examples 25 and 26

N-ethyl-5-fluoro-*N*-isopropyl-2-[7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]benzamide **25**

N-ethyl-5-fluoro-*N*-isopropyl-2-[7-(1-{[(1s,4s)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]benzamide **26**



Step 1

2-(7-{1-[(4-aminocyclohexyl)methyl]pyrrolidin-3-yl}imidazo[1,5-*a*]pyridin-5-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **25a**

Compound **24** (340 mg, 561.26 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **25a** (350 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 506.5 [M+1]

Step 2

N-ethyl-5-fluoro-*N*-isopropyl-2-[7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]benzamide **25**

N-ethyl-5-fluoro-*N*-isopropyl-2-[7-(1-{[(1s,4s)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]benzamide **26**

The crude product of Compound **25a** (347 mg) was dissolved in dichloromethane (5.0 mL), followed by the addition of ethanesulfonyl chloride (144.01 mg, 1.12 mmol) and triethylamine (283.33 mg, 2.80 mmol), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium carbonate solution (10 mL) was added to the reaction mixture. The mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 50%-80%) to obtain a mixture (100 mg), which was separated and purified by the preparative SFC (preparative column: DAICEL CHIRALPAK IF (250 mm * 50 mm,10 um), mobile phase: 25% n-hexane-ethanol (0.1% ammonia water)), to obtain the title Compounds **25** (1.69 mg, 2.83 μmol, yield: 1.69%) and **26** (1.95 mg, 3.26 μmol, yield: 1.95%).

Compound 25:

MS m/z (ESI): 598.5 [M+1]
SFC analysis: retention time: 4.613 min; chromatographic column: Chiralpak IF-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)/[ethanol +acetonitrile (0.05% isopropylamine)] = 80/20.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 – 7.62 (m, 2H), 7.52 – 7.29 (m, 4H), 7.04 – 6.93 (m, 1H), 6.59 – 6.43 (m, 1H), 3.30 – 3.17 (m, 3H), 3.07 – 2.76 (m, 6H), 2.74 – 2.56 (m, 2H), 2.36 – 2.12 (m, 3H), 1.92 – 1.67 (m, 6H), 1.28 – 1.14 (m, 7H), 1.00 – 0.63 (m, 9H).

Compound 26:

MS m/z (ESI): 598.4 [M+1]

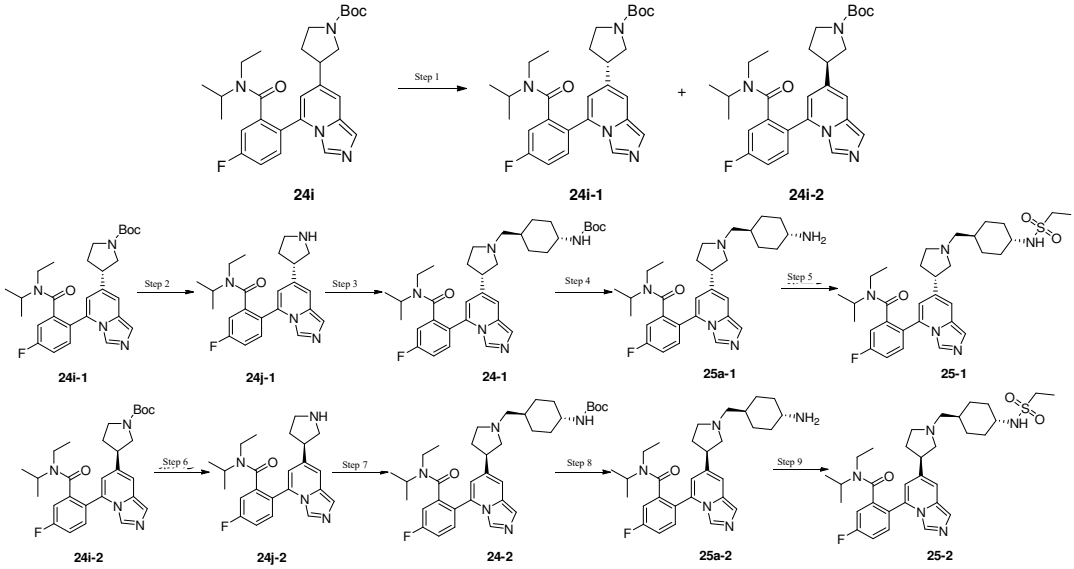
SFC analysis: retention time: 3.614 min; chromatographic column: Chiralpak IF-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)/[ethanol +acetonitrile (0.05% isopropylamine)] = 80/20.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 7.58 (m, 2H), 7.51 – 7.28 (m, 4H), 6.98 – 6.87 (m, 1H), 6.57 – 6.44 (m, 1H), 3.28 – 3.21 (m, 2H), 3.07 – 2.72 (m, 5H), 2.71 – 2.55 (m, 2H), 2.43 – 2.09 (m, 4H), 1.63 – 1.33 (m, 10H), 1.29 – 1.13 (m, 6H), 1.00 – 0.65 (m, 7H).

Examples 25-1 and 25-2

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*S*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*R*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25-2**



Step 1

(3*S*)-3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-tert-butyl formate **24i-1**

(3*R*)-3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-tert-butyl formate **24i-2**

Compound **24i** (300 mg, 606.6 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IC (250 mm * 30 mm,10 um), mobile phase: 0% to 50% (v/v) carbon dioxide-ethanol (0.1% ammonia water)), to obtain the title Compounds **24i-1** (100 mg, 202.2 μmol, yield: 33.3%) and **24i-2** (100 mg, 202.2 μmol, yield: 33.3%).

Single-configuration Compound 24i-1:

MS m/z (ESI):495.2 [M+1]

SFC analysis: retention time: 1.50 min; chromatographic column: Chiralpak IC-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2/EtOH (0.05% DEA) = 60/40.

Single-configuration Compound 24i-2:

MS m/z (ESI):495.2 [M+1]

SFC analysis: retention time: 2.0 min; chromatographic column: Chiralpak IC-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2/EtOH (0.05% DEA) = 60/40.

Steps 2 and 6

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*S*)-pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl]benzamide **24j-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*R*)-pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl]benzamide **24j-2**

Compound **24i-1**/**24i-2** (100 mg/100 mg, 202.2 μmol/202.2 μmol) was dissolved in methane dioxide (3.0 mL/3.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the

crude product of title Compound **24j-1/24j-2** (100 mg/100 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 24j-1:

MS m/z (ESI): 395.2 [M+1]

Single-configuration Compound 24j-2:

MS m/z (ESI): 395.2 [M+1]

Steps 3 and 7

N-[(1r,4r)-4-{[(3*S*)-3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **24-1**

N-[(1r,4r)-4-{[(3*R*)-3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **24-2**

The crude product of Compound **24j-1/24j-2** (100 mg/100 mg) was dissolved in methanol (2.0 mL/3.0 mL), followed by the addition of triethylamine (40 mg/40 mg, 395.3 μmol/395.3 μmol) and *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (53.64 mg/53.75 mg, 235.98 μmol/236.47 μmol), and the mixture was stirred at room temperature for (1.0/1.0) hour. Sodium cyanoborohydride (37.5 mg / 37.5 mg, 596.74 μmol/596.74 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for (11/11) hours. An aqueous sodium bicarbonate solution (10 mL/10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3/20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **24-1/24-2** (100 mg/100 mg, 165.08 μmol/165.08 μmol, yield: 83.94%/83.94%)

Single-configuration Compound 24-1:

MS m/z (ESI):606.5 [M+1]

SFC analysis: retention time: 1.16 min; chromatographic column: Chiralpak IC-3 50×4.6 mm I.D., 3 um; mobile phase: CO2/[IPA+ACN (0.05% DEA)] = 50/50.

Single-configuration Compound 24-2:

MS m/z (ESI):606.4 [M+1]

SFC analysis: retention time: 0.87 min; chromatographic column: Chiralpak IC-3 50×4.6 mm I.D., 3 um; mobile phase: CO2/[IPA+ACN (0.05% DEA)] = 50/50.

Steps 4 and 8

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*S*)-1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25a-1**

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*R*)-1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25a-2**

Compound **24-1/24-2** (100 mg/100 mg, 165.08 μmol/165.08 μmol) was dissolved in methane dioxide (2.0 mL/2.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **25a-1/25a-2** (100 mg/100 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 25a-1:

MS m/z (ESI): 506.2 [M+1]

Single-configuration Compound 25a-2:

MS m/z (ESI): 506.2 [M+1]

Steps 5 and 9

N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*S*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25-1**

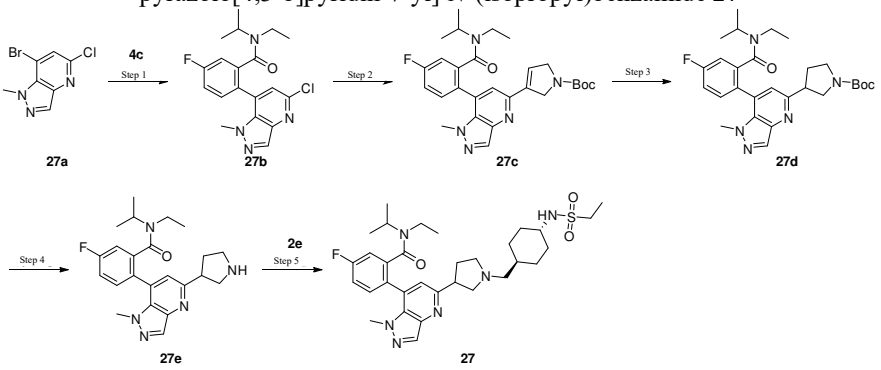
N-ethyl-5-fluoro-*N*-isopropyl-2-{7-[(3*R*)-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-*a*]pyridin-5-yl}benzamide **25-2**

The crude product of Compound **25a-1/25[a]-2** (100 mg/100 mg) was dissolved in dichloromethane (3.0 mL), followed by the addition of ethanesulfonyl chloride (32 mg/31.82 mg, 248.8 μmol/247.5 μmol) and triethylamine (85 mg/83.48, 840 μmol/825.0 μmol), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (20 mL), followed by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 0%-30%), to obtain the title Compound **25-1/25-2** (2.57 mg/2.99 mg, 4.30 μmol/5.0 μmol, yield: 2.66%/3.03%).

Single-configuration Compound 25-1:
MS m/z (ESI):598.4 [M+1]
Chiral HPLC: retention time: 5.45 min; chromatographic column: Chiralpak IA-3 50 x 4.6 mm I.D., 3 um; mobile phase: hexane (0.05% IPAm)/IPA+ACN (0.05% IPAm) = 85/15.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.09 – 7.61 (m, 2H), 7.52 – 7.27 (m, 4H), 6.99 (d, J = 7.6 Hz, 1H), 6.58 – 6.43 (m, 1H), 3.40 – 3.20 (m, 3H), 3.12 – 2.76 (m, 6H), 2.75 – 2.59 (m, 2H), 2.38 – 2.11 (m, 3H), 1.92 – 1.70 (m, 5H), 1.62 – 0.41 (m, 17H).
Single-configuration Compound 25-2:
MS m/z (ESI):598.4 [M+1]
Chiral HPLC: retention time: 4.85 min; chromatographic column: Chiralpak IA-3 50 x 4.6 mm I.D., 3 um; mobile phase: hexane (0.05% IPAm)/IPA+ACN (0.05% IPAm) = 85/15.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.09 – 7.60 (m, 2H), 7.53 – 7.28 (m, 4H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.58 – 6.44 (m, 1H), 3.46 – 3.19 (m, 3H), 3.18 – 2.78 (m, 6H), 2.76 – 2.61 (m, 2H), 2.40 – 2.09 (m, 3H), 1.94 – 1.70 (m, 5H), 1.68 – 0.31 (m, 17H)

Example 27

N-ethyl-5-fluoro-2-[1-methyl-5-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[4,3-b]pyridin-7-yl]-*N*-(isopropyl)benzamide **27**



Step 1

2-{5-chloro-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-7-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **27b**

7-Bromo-5-chloro-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine **27a**(450 mg, 1.83 mmol) and Compound **4c**(1.47 g, 2.19 mmol) were dissolved in dioxane (12 mL) and water (2.0 mL). Sodium carbonate (387 mg, 3.65 mmol) and $Pd(dppf)Cl_2$ (66.8 mg, 91.3 μmol) were added, and the mixture was stirred at 70°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the column chromatography (C18; mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 40%-60%), to obtain the title Compound **27b** (425 mg, 1.13 mmol, yield: 62.1%).
MS m/z (ESI): 375.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.69 (dd, *J* = 22.4, 15.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.32–7.19 (m, 1H), 3.85 – 3.51 (m, 4H), 3.27 – 2.62 (m, 2H), 1.14 – 0.37 (m, 9H).

Step 2

3-(7-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **27c**

Compound **27b**(300 mg, 533 μmol) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (189 mg, 640 μmol) were dissolved in dioxane (4.0 mL) and water (0.7 mL). Potassium carbonate (221 mg, 1.60 mmol) and $Pd(dppf)Cl_2$ (39.0 mg, 53.4 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **27c** (167 mg, 329 μmol, yield: 61.7%).
MS m/z (ESI): 508.25 [M+1]

Step 3

3-(7-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)pyrrolidin-1-tert-butyl formate **27d**

Compound **27c** (167 mg, 329 μmol) was dissolved in methanol (3.0 mL), followed by the addition of Pd/C (16.08 mg). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title

Compound **27d** (110 mg, 215 μmol, yield: 65.6%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 510.2 [M+1]

Step 4

N-ethyl-5-fluoro-2-[1-methyl-5-(yridinene-3-yl)-1H-pyrazolo[4,3-b]yridine-7-yl]-N-(propan-2-yl)benzamide

N-ethyl-5-fluoro-2-[1-methyl-5-(pyrrolidin-3-yl)-1*H*-pyrazolo[4,3-*b*]pyridin-7-yl]-*N*-isopropylbenzamide **27e**

Compound **27d** (110 mg, 216 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.6 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **27e** (134 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 410.2 [M+1]

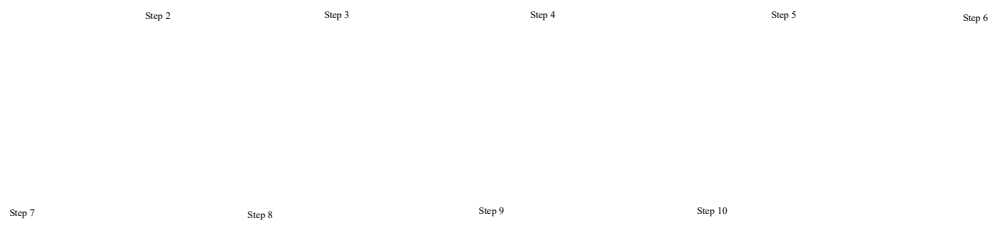
Step 5

N-ethyl-5-fluoro-2-[1-methyl-5-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-pyrazolo[4,3-b]pyridin-7-yl]-*N*-(isopropyl)benzamide **27**

The crude product of Compound **27e** (134 mg) and Compound **2e**(103 mg, 327 μmol) were dissolved in *N,N*-dimethylacetamide (2.0 mL), followed by the addition of potassium carbonate (135 mg, 0.98 mmol) and potassium iodide (54.3 mg, 327 μmol), and the mixture was stirred at 80°C for 16 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 25%-50%), to obtain the title Compound **27** (25.3 mg, 41.29 μmol, yield: 19.03 %) as white solid.
MS m/z (ESI): 613.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.11 (s, 0.49H), 7.57 (s, 1H), 7.39 (td, *J* = 8.8, 2.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.16 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 0.3H), 3.73 – 3.55 (m, 4.7H), 3.11 – 2.98 (m, 6H), 2.95 (dd, *J* = 14.8, 7.2 Hz, 4H), 2.64 (s, 2H), 2.31 (s, 1H), 2.13 (s, 1H), 1.85 (dd, *J* = 30.8, 12.0 Hz, 4H), 1.47 (s, 1H), 1.31 – 1.18 (m, 5H), 1.06 – 0.72 (m, 8H), 0.56 (s, 2H).

Example 29

N-[(1r,4r)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **29**



Step 1

3-bromo-5-chloropyridin-2-methyl carboxylate **29b**

3-Bromo-5-chloropyridin-2-carboxylic acid **29a** (20.0 g, 84.58 mmol) was dissolved in methanol (200 mL), and cooled to 0°C, followed by the addition of thionyl chloride (20.13 g, 169.17 mmol). The mixture was stirred at 0°C to allow for reacting for 5 min, warmed to 65°C and further stirred to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the residues was dissolved by adding dichloromethane (60 mL), and washed with a saturated aqueous sodium carbonate solution (40 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **29b** (19.5 g, 77.85 mmol, yield: 92.04%) as white solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 252.0 [M+1]

Step 2

(3-bromo-5-chloropyridin-2-yl)methanol **29c**

Compound **29b** (19.5 g, 77.85 mmol) was dissolved in methanol (200 mL) and tetrahydrofuran (200 mL), and cooled to 0°C, followed by the addition of sodium borohydride (15.0 g, 396.49 mmol). The mixture was stirred at room temperature to allow for reacting for 12.0 hour. The reaction mixture was cooled to 0°C, quenched by adding water

(100 mL), and extracted with ethyl acetate (200 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **29c** (16 g, 71.92 mmol, yield: 92.38%) as white solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 224.0 [M+1]

Step 3

2-[5-chloro-2-(hydroxymethyl)pyridin-3-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **29d**

Compound **29c** (6 g, 26.97 mmol), Compound **4c**(8.14 g, 24.27 mmol) and sodium carbonate (8.58 g, 80.91 mmol) were dissolved in dioxane (36 mL) and water (24 mL). Pd (dppf)Cl_2 (1.97 g, 2.70 mmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 20 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **29d** (4.6 g, 13.11 mmol, yield: 48.62%).
MS m/z (ESI): 351.1 [M+1]

Step 4

2-{5-chloro-2-[(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)methyl]pyridin-3-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **29e**

Compound **29d** (4.6 g, 13.11 mmol), 2,3-dihydro-1*H*-isoindol-1,3-dione (2.32 g, 15.73 mmol) and triphenylphosphine (5.16 g, 19.67 mmol) were dissolved in tetrahydrofuran (37 mL), under a nitrogen atmosphere, and cooled to 0°C, followed by the addition of DIAD (3.98 g, 19.67 mmol). The mixture was stirred at room temperature to allow for reacting for 12 hour. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **29e** (4 g, 8.33 mmol, yield: 63.6%) as yellow solid.
MS m/z (ESI): 480.1 [M+1]

Step 5

2-[2-(aminomethyl)-5-chloropyridin-3-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **29f**

Compound **29e** (4 g, 8.33 mmol) was dissolved in the solution of methylamine in ethanol (71.92 g, 694.72 mmol, 80.00 mL, 30%). The mixture was stirred at 65°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure, to obtain the crude product of title Compound **29f** (4.0 g) as yellow solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 350.3 [M+1]

Step 6

2-{6-chloro-3-methylimidazo[1,5-a]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **29g**

The crude product of Compound **29f** (4.0 g) was dissolved in acetic anhydride (40 mL), followed by the addition of p-toluenesulfonic acid (1.60 g, 9.29 mmol). The mixture was stirred at 100°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, poured into water (60 mL), regulated to be alkaline with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (100 mL x 3). The organic phases were combined, washed with saturated aqueous sodium carbonate solution (100 mL x 2), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **29g** (1.5 g, 4.01 mmol, yield: 35.1%).
MS m/z (ESI): 374.1 [M+1]

Step 7

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **29h**

Compound **29g** (1.5 g, 4.01 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (1.77 g, 5.99 mmol) and cesium carbonate (4.00 g, 12.28 mmol) were dissolved in dioxane (15 mL) and water (5 mL). Pd(dtbpf)Cl_2 (261.50 mg, 401.23 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **29h** (1.8 g, 3.55 mmol, yield: 88.6%).
MS m/z (ESI): 507.3 [M+1]

Step 8

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **29i**

Compound **29h** (600 mg, 1.18 mmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (143.8 mg, 1.18 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **29i** (400 mg, 786.4 μmol, yield: 66.4%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 509.2 [M+1]

Step 9

N-ethyl-5-fluoro-2-[3-methyl-6-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **29j**

Compound **29i** (400 mg, 786.4 μmol) was dissolved in dichloromethane (6 mL), followed by the addition of trifluoroacetic acid (2.37 g, 20.77 mmol, 1.60 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **29j** (400 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.6 [M+1]

Step 10

N-[(1r,4r)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **29**

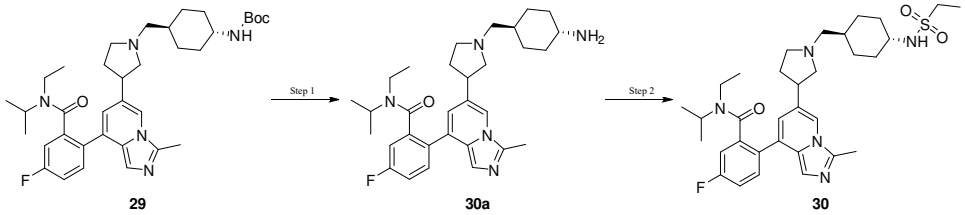
The crude product of Compound **29j** (70 mg, 134 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (60.90 mg, 267.93 μmol) and triethylamine (67.78 mg, 669.81 μmol) were dissolved in methanol (3.0 mL), and stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (12.63 mg, 200.94 μmol) was added, and the mixture was stirred at room temperature for 2.0 hours. The reaction mixture was diluted by adding dichloromethane (30 mL), followed by the addition of a saturated aqueous sodium carbonate solution (20 mL), and the mixture was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **29** (12.1 mg, 19.52 μmol, yield: 14.57 %) as white solid.

MS m/z (ESI): 620.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 – 7.96 (m, 1H), 7.72 – 7.59 (m, 1H), 7.47 – 7.22 (m, 2H), 7.05 (s, 1H), 6.82 – 6.59 (m, 2H), 3.13 – 2.80 (m, 7H), 2.65 – 2.57 (m, 2H), 2.36 – 2.24 (m, 1H), 2.17 – 2.00 (m, 1H), 1.85 – 1.72 (m, 3H), 1.65 – 1.48 (m, 2H), 1.37 (s, 9H), 1.27 – 1.10 (m, 7H), 1.08 – 0.97 (m, 3H), 0.92 – 0.66 (m, 4H), 0.58 – 0.48 (m, 1H), 0.37 – 0.17 (m, 3H).

Example 30

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **30**



Step 1

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **30a**

Compound **29** (150 mg, 242 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (275.95 mg, 2.42 mmol, 186.45 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **30a** (150 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 520.5 [M+1]

Step 2

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **30**

The crude product of Compound **30a** (150 mg) was dissolved in dichloromethane (3.0 mL), and cooled to 0°C, followed by the addition of ethanesulfonyl chloride (60.9 mg, 473.40 μmol) and triethylamine (119.76 mg, 1.18

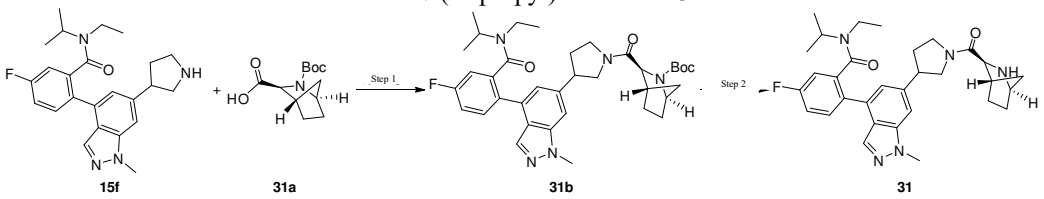
mmol, 164.96 μL). The mixture was stirred at room temperature for 12 hours. Water (20 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (20 mL x 2). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%), to obtain the title Compound **30** (23.96 mg, 39.16 μmol, yield: 16.55 %) as white solid.

MS m/z (ESI): 612.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.69 – 7.60 (m, 1H), 7.40 – 7.26 (m, 2H), 7.03 – 6.96 (m, 2H), 6.68 – 6.61 (m, 1H), 3.44 – 3.39 (m, 1H), 3.30 – 3.23 (m, 2H), 3.10 – 2.71 (m, 6H), 2.66 – 2.55 (m, 5H), 2.42 – 2.32 (m, 1H), 2.29 – 2.12 (m, 3H), 1.92 – 1.68 (m, 5H), 1.38 – 1.01 (m, 7H), 0.98 – 0.70 (m, 7H), 0.34 – 0.25 (m, 2H).

Example 31

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]pyrrolidin-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **31**



Step 1

(1*R*,3*S*,4*S*)-3-[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-carbonyl]-2-azabicyclo[2.2.1]heptan-2-tert-butyl carboxylate **31b**

Compound **15f** (31.9 mg, 78.1 μmol), (1*R*, 3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.1]heptan-3-carboxylic acid **31a**(18.8 mg, 78.1 μmol) and *N,N*-diisopropylethylamine (89.6 mg, 693 μmol) were dissolved in DMF (1 mL), and cooled to 0°C. EDCI (19.4 mg, 101 μmol) and HOBt (12.6 mg, 93.7 μmol) were added, and the mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **31b** (35 mg, 55.4 μmol, yield: 70.8%) as white solid.

MS m/z (ESI): 632.25 [M+1]

Step 2

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]pyrrolidin-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **31**

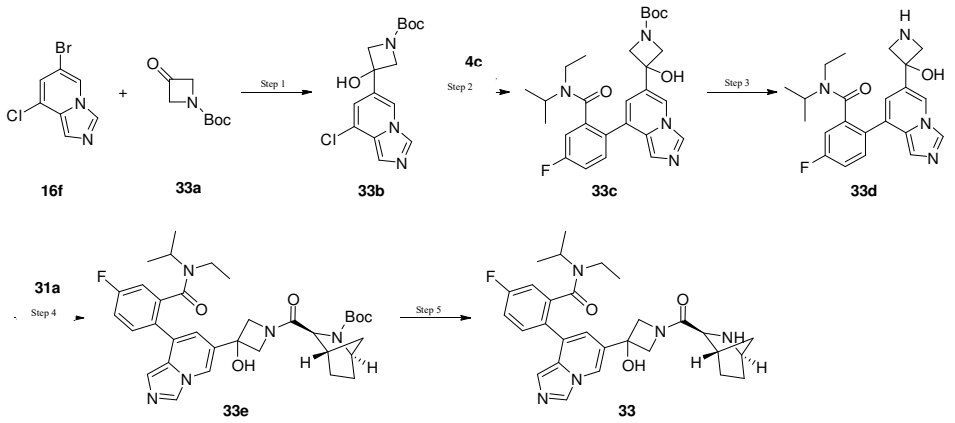
Compound **31b** (31.0 mg, 49.0 μmol) was dissolved in methane dioxide (0.9 mL) and trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 40%-55%), to obtain the title Compound **31** (10.0 mg, 18.8 μmol, yield: 76.6%) as white solid.

MS m/z (ESI): 532.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 4.0 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.44 – 7.27 (m, 2H), 7.13 – 7.03 (m, 1H), 4.29 – 4.10 (m, 0.46H), 4.05 (d, J = 2.8 Hz, 4H), 3.93 (dt, J = 21.2, 12.8 Hz, 1H), 3.84 – 3.54 (m, 4.61H), 3.33 (ddd, J = 42.4, 12.8, 7.6 Hz, 3H), 2.89 – 2.69 (m, 2H), 2.33 (dd, J = 19.6, 17.6 Hz, 1H), 2.14 (ddd, J = 27.6, 18.8, 8.4 Hz, 1H), 1.67 – 1.32 (m, 6H), 1.09 – 0.52 (m, 7H), 0.08 (dd, J = 14.8, 6.8 Hz, 2H).

Example 33

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]-3-hydroxylazacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **33**



Step 1

3-{8-chloroimidazo[1,5-a]pyridin-6-yl}-3-hydroxylazacyclobutan-1-tert-butyl carboxylate **33b**

Compound **16f** (1.7 g, 7.34 mmol) was dissolved in tetrahydrofuran (20 mL), and cooled to 0°C, followed by the addition of the solution of *i*-PrMgCl.LiCl in tetrahydrofuran (1.3 M, 8.47 mL). The mixture was stirred at 0°C to allow for reacting for 10 min, and then, 3-oxoazacyclobutan-1-tert-butyl carboxylate (1.51 g, 8.81 mmol) was added. The mixture was stirred at room temperature to allow for reacting for 2.0 hour. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (30 mL), and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **33b** (950 mg, 2.93 mmol, yield: 39.95%).

MS m/z (ESI): 324.0 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 – 8.46 (m, 2H), 7.44 (s, 1H), 7.00 (d, J = 1.0 Hz, 1H), 6.60 (s, 1H), 4.16 – 3.96 (m, 4H), 1.41 (s, 9H).

Step 2

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-3-hydroxylazacyclobutan-1-tert-butyl carboxylate **33c**

Compound **33b** (300 mg, 926.57 μmol) and Compound **4c**(465.91 mg, 1.39 mmol) were dissolved in dioxane (5.0 mL) and water (1.0 mL). Potassium phosphate (590.04 mg, 2.78 mmol) and Pd(dtbpf)Cl_2 (60.39 mg, 92.66 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (25 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **33c** (230 mg, 463.18 μmol, yield: 49.99%).

MS m/z (ESI): 497.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br d, J = 3.1 Hz, 2H), 7.70 (dd, J = 5.6, 8.6 Hz, 1H), 7.44 – 7.28 (m, 2H), 7.15 (s, 1H), 6.82 – 6.71 (m, 1H), 6.55 (s, 1H), 4.09 – 3.91 (m, 4H), 3.48 (td, J = 6.5, 13.2 Hz, 1H), 3.28 – 3.22 (m, 1H), 2.98 (br dd, J = 6.9, 13.4 Hz, 1H), 1.40 (s, 9H), 0.97 – 0.74 (m, 7H), 0.33 (br d, J = 6.4 Hz, 2H).

Step 3

N-ethyl-5-fluoro-2-[6-(3-hydroxylazacyclobutan-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl) benzamide **33d**

Compound **33c**(110 mg, 221.52 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **33d** (110 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 397.2 [M+1]

Step 4

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]- 4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-3-hydroxylazacyclobutan-1-carbonyl]-2-azabicyclo[2.2.1]heptan-2-tert-butyl carboxylate **33e**

Compound **31a** (57 mg, 236.24 μmol), *N,N*-diisopropylethylamine (90 mg, 696.36 μmol), EDCI(62 mg, 323.42 μmol) and HOBt(44 mg, 325.63 μmol) were dissolved in dichloromethane (2 mL), followed by the addition of the crude product of Compound **33d** (110 mg), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then

extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient:22%-52%), to obtain the title Compound **33e** (100 mg, 161.4 μmol, yield: 75.6%) as white solid.
MS m/z (ESI): 620.3 [M+1]

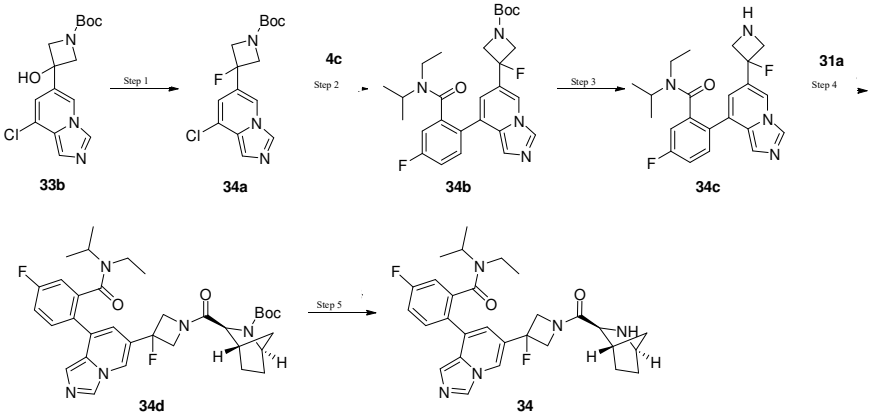
Step 5

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]-3-hydroxylazacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **33**

Compound **33e** (100 mg, 161.36 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 15%-45%), to obtain the title Compound **33** (32.76 mg, 63.05 μmol, yield: 39.07 %).
MS m/z (ESI): 520.0 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 – 8.42 (m, 2H), 7.76 – 7.65 (m, 1H), 7.44 – 7.28 (m, 2H), 7.21 – 7.11 (m, 1H), 6.86 – 6.57 (m, 2H), 4.64 – 3.89 (m, 5H), 3.50 – 3.43 (m, 1H), 3.28 – 3.16 (m, 2H), 3.10 – 2.88 (m, 1H), 1.76 – 0.63 (m, 14H), 0.35 – 0.25 (m, 2H).

Example 34

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]-3-fluoroazacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **34**



Step 1

3-{8-chloroimidazo[1,5-a]pyridin-6-yl}-3-fluoroazacyclobutan-1-tert-butyl carboxylate **34a**

Compound **33b** (300 mg, 926.57 μmol) was dissolved in dichloromethane (5.0 mL), and cooled to -60°C, followed by the dropwise addition of DAST(298.71 mg, 1.85 mmol, 0.5 mL). The mixture was stirred -60°C to allow for reacting for 1.0 hour, and then slowly warmed to room temperature, at which the mixture was stirred to allow for reacting for 1.0 hour. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (20 mL), and extracted with dichloromethane (30 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **34a** (235 mg, 721.4 μmol, yield: 77.9%) as brown solid.
MS m/z (ESI): 326.0 [M+1]

Step 2

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-3-fluoroazacyclobutan-1-tert-butyl carboxylate **34b**

Compound **34a** (235 mg, 721.38 μmol) and Compound **4c**(485 mg, 1.45 mmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). Potassium phosphate (460 mg, 2.17 mmol) and Pd(dtbpf)Cl_2 (48 mg, 73.65 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (25 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **34b** (240 mg, 481.38 μmol, yield: 66.7 %).
MS m/z (ESI): 499.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.46 (s, 1H), 7.70 (dd, J = 5.5, 8.6 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.24 – 7.19 (m, 1H), 6.74 – 6.67 (m, 1H), 4.41 – 4.22 (m, 4H), 3.51 – 3.44 (m, 1H), 3.34 – 3.26 (m, 1H), 2.91 (br dd, J = 6.9, 13.6 Hz, 1H), 1.40 (s, 9H), 1.00 – 0.68 (m, 7H), 0.33 (br d, J = 6.6 Hz, 2H).

Step 3

N-ethyl-5-fluoro-2-[6-(3-fluoroazacyclobutan-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **34c**

Compound **34b** (230 mg, 461.33 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (2.22 g, 19.47 mmol, 1.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **34c** (200 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 399.1 [M+1]

Step 4

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]- 4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-3-fluoroazacyclobutan-1-carbonyl]-2-azabicyclo[2.2.1]heptan-2-tert-butyl carboxylate **34d**

Compound **31a** (57 mg, 236.24 μmol), *N,N*-diisopropylethylamine (85 mg, 657.69 μmol), EDCI(62 mg, 323.42 μmol) and HOBt(41 mg, 303.43 μmol) were dissolved in dichloromethane (3 mL), followed by the addition of the crude product of Compound **34c** (100 mg), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **34d** (100 mg, 160.85 μmol, yield: 82.43%) as white solid.
MS m/z (ESI): 622.4 [M+1]

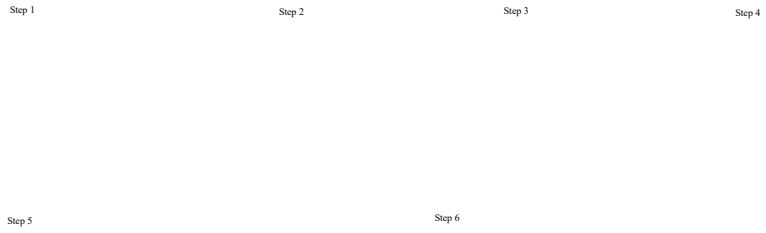
Step 5

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]-3-fluoroazacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **34**

Compound **34d** (100 mg, 160.85 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 25%-55%), to obtain the title Compound **34** (45.77 mg, 87.75 μmol, yield: 54.56 %).
MS m/z (ESI): 522.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 – 8.64 (m, 1H), 8.46 (s, 1H), 7.77 – 7.65 (m, 1H), 7.46 – 7.30 (m, 2H), 7.28 – 7.18 (m, 1H), 6.79 – 6.70 (m, 1H), 4.87 – 4.54 (m, 2H), 4.47 – 4.16 (m, 2H), 3.51 – 3.39 (m, 2H), 3.25 – 3.22 (m, 1H), 3.02 – 2.62 (m, 2H), 1.57 – 0.65 (m, 14H), 0.36 – 0.30 (m, 2H).

Example 35

N-ethyl-5-fluoro-2-[3-methyl-7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]-*N*-(isopropyl)benzamide **35**



Step 1

2-[4-chloro-6-(acetamidomethyl)pyridin-2-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **35a**

Compound **24f** (4.1 g, 11.72 mmol) and triethylamine (3.56 g, 35.16 mmol) were dissolved in dichloromethane (50 mL), followed by the dropwise addition of acetyl chloride (1.38 g, 17.58 mmol, 1.07 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (40 mL x 3). The organic phases were combined, washed with saturated brine (30 mL x 2), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product

of title Compound **35a** (5.4 g). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 392.2 [M+1]

Step 2

2-{7-chloro-3-methylimidazo[1,5-a]pyridin-5-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **35b**

The crude product of Compound **35a** (5.5 g) was dissolved in toluene (40 mL), followed by the addition of phosphorus oxychloride (10.76 g, 70.18 mmol, 8 mL). The mixture was stirred at 100℃ to allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. A saturated aqueous sodium bicarbonate solution (100 mL) was added to the reaction mixture, which was then extracted with dichloromethane (80 mL x 3). The organic phases were combined, washed with saturated brine (50 mL x 2), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **35b** (1.4 g, 3.74 mmol, yield: 26.7%) as yellow solid.
MS m/z (ESI): 374.1[M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 – 7.64 (m, 2H), 7.47 – 7.37 (m, 2H), 7.27 (br d, J = 2.4 Hz, 1H), 6.44 – 6.36 (m, 1H), 5.75 (s, 1H), 3.81 – 3.69 (m, 1H), 3.04 – 2.90 (m, 1H), 1.99 – 1.92 (m, 3H), 1.13 – 1.03 (m, 5H), 0.91 (d, J = 6.8 Hz, 1H), 0.67 (br t, J = 6.8 Hz, 3H).

Step 3

3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-7-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **35c**

Compound **35b** (900 mg, 2.41 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (852.74 mg, 2.89 mmol) and potassium phosphate (1.28 g, 6.04 mmol) were dissolved in dioxane (15 mL) and water (1.8 mL). Pd(dtbpf)Cl_2 (161.61 mg, 247.96 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 80°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (30 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **35c** (740 mg, 1.46 mmol, yield: 60.7%).
MS m/z (ESI): 507.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (br d, J = 6.1 Hz, 1H), 7.47 – 7.28 (m, 4H), 6.75 – 6.65 (m, 1H), 6.33 (br s, 1H), 4.38 (br d, J = 4.5 Hz, 2H), 4.18 (br d, J = 4.4 Hz, 2H), 3.78 (br d, J = 1.3 Hz, 1H), 3.20 (br s, 1H), 2.99 – 2.85 (m, 1H), 2.02 – 1.93 (m, 3H), 1.44 (br d, J = 9.4 Hz, 9H), 1.11 – 0.95 (m, 6H), 0.86 – 0.79 (m, 1H), 0.60 (br t, J = 6.6 Hz, 2H).

Step 4

3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-7-yl)pyrrolidin-1-tert-butyl formate **35d**

Compound **35c** (140 mg, 276.35 μmol) was dissolved in methanol (10 mL), followed by the addition of 10% Pd/C (29.41 mg, 276.35 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **35d** (130 mg, 255.6 μmol, yield: 92.5%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 509.2 [M+1]

Step 5

N-ethyl-5-fluoro-2-[3-methyl-7-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]-*N*-(isopropyl)benzamide **35e**

Compound **35d** (130 mg, 255.6 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **35e** (110 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 409.3 [M+1]

Step 6

N-ethyl-5-fluoro-2-[3-methyl-7-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-5-yl]-*N*-(isopropyl)benzamide **35**

The crude product of Compound **35e** (50.0 mg, 95.69 μmol, trifluoroacetate) was dissolved in *N,N*-dimethylformamide (1 mL), followed by the addition of [(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl 4-methylphenyl-1-sulfonate **35f**(50 mg, 133.15 μmol), potassium carbonate (26.45 mg, 191.38 μmol) and TBAI(3.53 mg, 9.57 μmol), and the mixture was stirred at 90°C for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated

under a reduced pressure, and the resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **35** (2.88 mg, 4.71 μmol, yield: 4.92%).
MS m/z (ESI): 612.3 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.70 – 7.51 (m, 1H), 7.45 – 7.14 (m, 4H), 6.67 – 6.34 (m, 1H), 4.05 – 3.62 (m, 1H), 3.27 – 3.21 (m, 1H), 3.15 – 2.99 (m, 4H), 2.93 – 2.57 (m, 3H), 2.49 – 2.24 (m, 3H), 2.18 – 2.07 (m, 2H), 2.05 – 1.97 (m, 2H), 1.95 – 1.82 (m, 3H), 1.74 – 1.60 (m, 1H), 1.48 – 1.25 (m, 8H), 1.22 – 0.98 (m, 9H), 0.90 – 0.81 (m, 2H).

Example 36

N-ethyl-5-fluoro-2-{1-methyl-6-[4-({[(1*r*,4*r*)-4-(2-oxo-1,3-oxazolidin-3-yl)cyclohexyl]methyl}amino)piperidin-1-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **36**

Step 1

N-[1-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl]tert-butyl carbamate **36a**

Compound **15c** (500 mg, 936 μmol) and *N*-(piperidin-4-yl)tert-butyl carbamate (187 mg, 936 μmol) were dissolved in toluene (10.5 mL) and tertiary butanol (3.5 mL). $Pd(Oac)_2$ (21.0 mg, 93.6 μmol), Xphos(89.3 mg, 187 μmol) and sodium tert-butoxide (89.3 mg, 187 μmol) were added, and the mixture was stirred at 120°C under a nitrogen atmosphere to allow for reacting for 8.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **36a** (454 mg, 844.4 μmol, yield: 90.2%) as white solid.
MS m/z (ESI): 538.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 5.2 Hz, 1H), 7.59 (ddd, J = 8.4, 5.6, 2.8 Hz, 1H), 7.36 (td, J = 8.4, 2.8 Hz, 1H), 7.28 (td, J = 9.6, 2.8 Hz, 1H), 6.94 – 6.80 (m, 3H), 3.95 (d, J = 3.6 Hz, 3H), 3.71 (d, J = 3.2 Hz, 2H), 3.38 (dd, J = 13.2, 6.4 Hz, 2H), 3.27 (dt, J = 13.6, 6.8 Hz, 1H), 2.83 (dt, J = 24.8, 9.2 Hz, 3H), 1.83 (d, J = 11.2 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.39 (s, 9H), 0.85 (d, J = 6.4 Hz, 3H), 0.70 (dt, J = 33.2, 7.2 Hz, 4H), 0.13 (d, J = 6.4 Hz, 2H).

Step 2

2-[6-(4-aminopiperidin-1-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **36b**

Compound **36a** (200 mg, 371.98 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.8 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **36b** (430 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 438.1 [M+1]

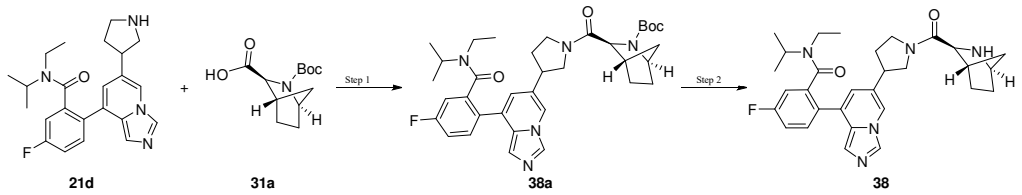
Step 3

N-ethyl-5-fluoro-2-{1-methyl-6-[4-({[(1*r*,4*r*)-4-(2-oxo-1,3-oxazolidin-3-yl)cyclohexyl]methyl}amino)piperidin-1-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **36**

The crude product of Compound **36b** (150 mg) was dissolved in dichloromethane (2.0 mL), followed by the addition of Compound **28c** (25.2 mg, 128 μmol), and the mixture was stirred at 0°C for 0.5 hours. Sodium triacetoxyborohydride (81.3 mg, 383 μmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 30%-45%), to obtain the title Compound **36** (19.5 mg, 31.5 μmol, yield: 45.4 %) as white solid.
MS m/z (ESI): 619.25 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.69 – 7.64 (m, 1H), 7.62 – 7.56 (m, 1H), 7.37 (td, J = 8.8, 2.8 Hz, 1H), 7.32 – 7.24 (m, 1H), 6.92 (s, 1H), 6.87 – 6.83 (m, 1H), 4.27 – 4.20 (m, 2H), 3.97 – 3.94 (m, 3H), 3.73 (s, 2H), 3.51 – 3.42 (m, 3H), 3.41 – 3.34 (m, 1H), 3.28 (dd, J = 13.6, 6.8 Hz, 1H), 2.88 – 2.70 (m, 4H), 2.55 (d, J = 6.4 Hz, 2H), 1.92 (dd, J = 40.0, 11.6 Hz, 4H), 1.68 (d, J = 10.4 Hz, 2H), 1.43 (dd, J = 22.0, 12.0 Hz, 5H), 1.09 – 0.63 (m, 9H), 0.12 (d, J = 6.8 Hz, 2H).

Example 38

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]pyrrolidin-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **38**



Step 1

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-6-yl)pyrrolidin-1-carbonyl]-2-azabicyclo[2.2.1]heptan-2-tert-butyl carboxylate **38a**

Compound **31a** (54 mg, 223.80 μmol) and *N,N*-diisopropylethylamine (80 mg, 619 μmol) were dissolved in dichloromethane (2 mL), and cooled to 0°C, followed by the addition of EDCI (58 mg, 302.55 μmol) and HOBt (41 mg, 303.4 μmol). Compound **21d** (102 mg, 200.6 μmol, trifluoroacetate) was then added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **38a** (80 mg, 129.5 μmol, yield: 64.6%).

MS m/z (ESI): 618.4 [M+1]

Step 2

2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]pyrrolidin-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **38**

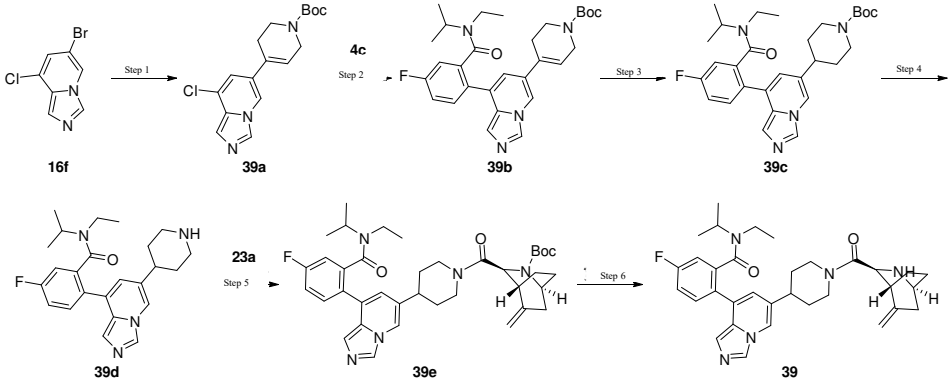
Compound **38a** (80 mg, 129.5 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%), to obtain the title Compound **38** (17.7 mg, 34.2 μmol, yield: 26.4 %).

MS m/z (ESI): 518.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.35 (m, 1H), 8.34 – 8.26 (m, 1H), 7.74 – 7.64 (m, 1H), 7.44 – 7.28 (m, 2H), 7.17 – 7.09 (m, 1H), 6.77 – 6.62 (m, 1H), 4.29 – 3.55 (m, 3H), 3.54 – 3.40 (m, 2H), 3.28 – 3.18 (m, 3H), 3.01 – 2.66 (m, 2H), 2.42 – 1.77 (m, 3H), 1.56 – 0.68 (m, 14H), 0.30 – 0.22 (m, 2H).

Example 39

N-ethyl-5-fluoro-2-(6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]piperidin-4-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **39**



Step 1

4-{8-chloroimidazo[1,5-*a*]pyridin-6-yl}-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **39a**

Compound **16f** (500 mg, 2.16 mmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (560 mg, 1.81 mmol) and sodium carbonate (686.8 mg, 6.48 mmol) were dissolved in dioxane (10 mL) and water (2 mL). Pd (dppf)Cl_2 (158 mg, 216 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **39a** (400 mg, 1.20 mmol, yield: 55.5%).

MS m/z (ESI): 334.1 [M+1]

Step 2

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl formate **39b**

Compound **39a** (400 mg, 1.20 mmol) and Compound **4c** (600 mg, 1.79 mmol) were dissolved in dioxane (12 mL) and water (4.0 mL). Cesium carbonate (1.17 g, 3.59 mmol) and Pd(dtbpf)Cl_2 (78.1 mg, 119.8 μmol) were added, and the mixture was stirred at 95 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **39b** (400 mg, 789.6 μmol, yield: 65.9%).

MS m/z (ESI): 507.3 [M+1]

Step 3

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)piperidin-1-tert-butyl formate **39c**

Compound **39b** (400 mg, 789.6 μmol) was dissolved in methanol (20 mL), followed by the addition of Pd/C (96 mg, 790 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **39c** (300 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 509.5 [M+1]

Step 4

N-ethyl-5-fluoro-2-[6-(piperidin-4-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **39d**

Compound **39c** (300 mg, 589.8 μmol) was dissolved in dichloromethane (4 mL), followed by the addition of trifluoroacetic acid (134.50 mg, 1.18 mmol, 90.88 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **39d** (230 mg, 563.02 μmol, yield: 95.5%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.2 [M+1]

Step 5

(1*S*,3*S*,4*R*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)piperidin-1-carbonyl]-5-methylene-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **39e**

Compound **39d** (100.0 mg, 244.8 μmol), (1*S*,3*S*,4*R*)-2-tert-butoxycarbonyl-5-methylene-2-azabicyclo[2.2.2]octan-3-carboxylic acid **23a** (40.00 mg, 149.63 μmol) and *N,N*-diisopropylethylamine (126.55 mg, 979.17 μmol) were dissolved in dichloromethane (4 mL), and cooled to 0°C. EDCI (70.39 mg, 367.19 μmol) and HOBt (56.23 mg, 367.19 μmol) were added, and the mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **39e** (50 mg, 76.01 μmol, yield: 31.05 %) as white solid.

MS m/z (ESI): 658.4 [M+1]

Step 6

N-ethyl-5-fluoro-2-(6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]piperidin-4-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **39**

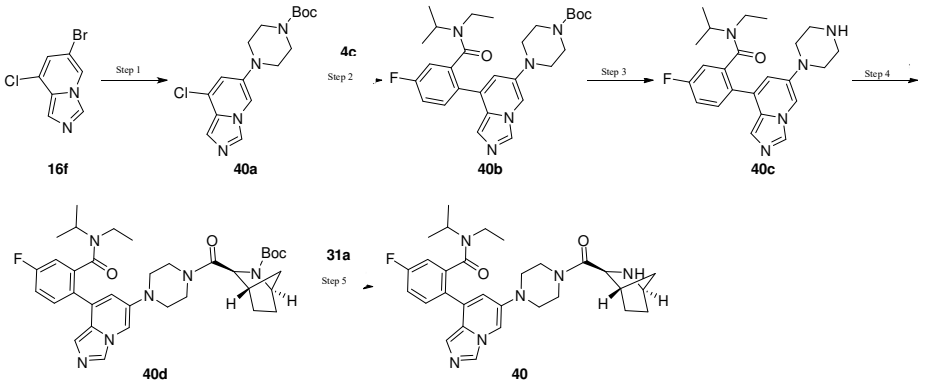
Compound **39e** (50 mg, 76.01 μmol) was dissolved in methane dioxide (2.0 mL) and trifluoroacetic acid (8.67 mg, 76.01 μmol, 5.86 μL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 32%-62%), to obtain the title Compound **39** (11.53 mg, 20.67 μmol, yield: 27.2 %).

MS m/z (ESI): 558.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (br d, J = 7.9 Hz, 1H), 8.28 – 8.18 (m, 1H), 7.74 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.16 – 7.08 (m, 1H), 6.68 – 6.57 (m, 1H), 4.92 (br d, J = 13.6 Hz, 1H), 4.73 (s, 1H), 4.65 – 4.53 (m, 1H), 3.94 – 3.72 (m, 2H), 3.53 – 3.40 (m, 2H), 3.24 – 3.00 (m, 3H), 2.73 (br d, J = 8.3 Hz, 2H), 2.40 – 2.22 (m, 2H), 2.01 – 1.74 (m, 2H), 1.72 – 1.35 (m, 7H), 0.97 – 0.65 (m, 7H), 0.32 – 0.13 (m, 3H).

Example 40

2-(6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1] heptan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **40**



Step 1

4-{8-chloroimidazo[1,5-*a*]pyridin-6-yl}-piperazin-1-tert-butyl carboxylate **40a**

Compound **16f** (500 mg, 2.16 mmol), piperazin-1-tert-butyl carboxylate (403 mg, 2.16 mmol), Puphos(101 mg, 216.44 μmol) and cesium carbonate (2.11 g, 6.48 mmol) were dissolved in dioxane (10 mL). $Pd_2(dba)_3$ (158 mg, 216 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (35 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **40a** (200 mg, 593.80 μmol, yield: 27.5%).

MS m/z (ESI): 337.1 [M+1]

Step 2

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-piperazin-1-tert-butyl formate **40b**

Compound **40a** (150 mg, 445.35 μmol) and Compound **4c** (300 mg, 894.93 μmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). Potassium phosphate (284 mg, 1.34 mmol) and $Pd(dtbpf)Cl_2$ (30 mg, 46.03 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (35 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **40b** (100 mg, 196.23 μmol, yield: 44.1%).

MS m/z (ESI): 510.2 [M+1]

Step 3

N-ethyl-5-fluoro-2-[6-(piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **40c**

Compound **40b** (100 mg, 196.23 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **40c** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 410.1 [M+1]

Step 4

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.1]heptan-2-tert-butyl carboxylate **40d**

Compound **31a** (52.23 mg, 216.45 μmol) and *N,N*-diisopropylethylamine (176.42 mg, 1.37 mmol, 237.76 μL) were dissolved in dichloromethane (3 mL), and cooled to 0°C, followed by the addition of EDCI (56.45 mg, 294.45 μmol) and HOBt(40.31 mg, 298.35 μmol). The crude product of Compound **40c** (100 mg) was then added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%), to obtain the title Compound **40d** (80 mg, 126.43 μmol, yield: 64.4%).

MS m/z (ESI): 633.4 [M+1]

Step 5

2-(6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **40**

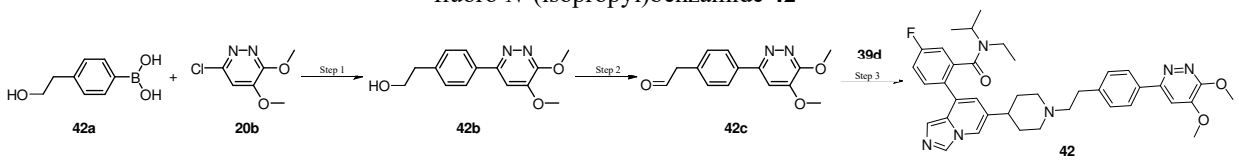
Compound **40d** (80 mg, 126.4 μmol) was dissolved in methane dioxide (1.5 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 25%-55%), to obtain the title Compound **40** (53.1 mg, 93.3 μmol, yield: 46.2 %).

MS m/z (ESI): 533.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.83 (s, 1H), 7.72 – 7.63 (m, 1H), 7.44 – 7.28 (m, 2H), 7.11 – 7.02 (m, 1H), 6.71 – 6.62 (m, 1H), 3.76 – 3.38 (m, 8H), 3.07 – 2.86 (m, 5H), 2.42 (s, 1H), 1.54 – 1.30 (m, 4H), 1.26 – 0.98 (m, 3H), 0.98 – 0.67 (m, 7H), 0.34 – 0.26 (m, 2H).

Example 42

2-[6-(1-{2-[4-(5,6-dimethoxypyridazin-3-yl)phenyl]ethyl}piperidin-4-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **42**



Step 1

2-[4-(5,6-dimethoxypyridazin-3-yl)phenyl]ethyl-1-ol **42b**

[4-(2-hydroxyethyl)phenyl]boric acid **42a** (855.65 mg, 5.16 mmol) and 6-chloro-3,4-dimethoxypyridazine **20b** (900 mg, 5.16 mmol) were dissolved in dioxane (10 mL) and water (2.0 mL). Sodium carbonate (1.09 g, 10.31 mmol) and tetrakis(triphenylphosphine)palladium (595.70 mg, 515.51 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 3.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **42b** (1.23 g, 4.73 mmol, yield: 91.7%) as white solid.

MS m/z (ESI): 261.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 4.68 (t, J = 5.2 Hz, 1H), 4.05 (s, 2H), 3.98 (s, 2H), 3.65 (td, J = 7.2, 5.6 Hz, 1H), 2.79 (t, J = 6.8 Hz, 1H).

Step 2

2-[4-(5,6-dimethoxypyridazin-3-yl)phenyl]acetaldehyde **42c**

Compound **42b** (40 mg, 153.68 μmol) was dissolved in dichloromethane (2.0 mL). The mixture was cooled to 0°C, and a Dess-Martin oxidizing agent (84.73 mg, 199.78 μmol) was added. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using ethyl acetate/petroleum ether as an elution system, to obtain the title Compound **42c** (26.27 mg, 101.71 μmol, yield: 66.2%) as yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (t, J= 1.6 Hz, 1H), 8.07 (d, J= 8.0 Hz, 2H), 7.61 (s, 1H), 7.39 (d, J= 8.0 Hz, 2H), 4.06 (s, 3H), 3.99 (s, 3H), 3.87 (d, J= 1.6 Hz, 2H).

Step 3

2-[6-(1-{2-[4-(5,6-dimethoxypyridazin-3-yl)phenyl]ethyl}piperidin-4-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **42**

Compound **39d** (71.18 mg, 174.23 μmol), triethylamine (58.77 mg, 580.78 μmol, 80.73 μL) and Compound **42c** (50 mg, 193.59 μmol) were dissolved in methanol (0.9 mL), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (24.33 mg, 387.19 μmol) was added, and the mixture was stirred at room temperature for 0.5 hours. An aqueous sodium bicarbonate solution (5.0 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (5 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 34%-64%), to obtain the title Compound **42** (5.70 mg, 8.76 μmol, yield: 4.52%) as offwhite solid.

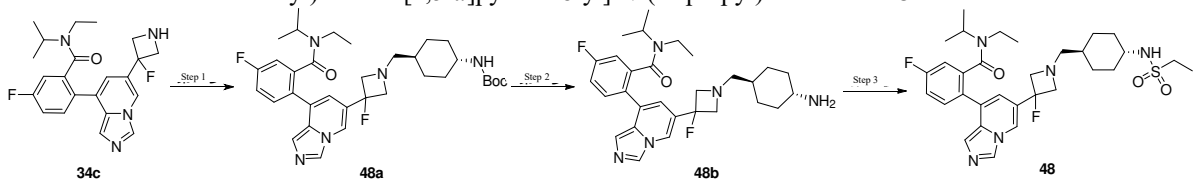
MS m/z (ESI): 651.5 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.69 – 7.60 (m, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.23 – 7.11 (m, 3H), 6.82 – 6.78 (m, 1H), 4.24 (s, 3H), 4.02 (s, 3H), 3.63 – 3.37 (m, 2H), 3.30 – 3.17 (m, 2H), 3.02 – 2.93 (m, 3H), 2.82 – 2.71 (m, 2H), 2.54 – 2.44 (m, 1H), 2.32 – 2.17 (m, 2H), 2.01 – 1.83 (m, 4H), 0.79 (m, J = 9.52 Hz, 7H), 0.24 (d, J = 6.8 Hz, 2H).

Example 48

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}azacyclobutan-3-

yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **48**



Step 1

N-[(1r,4r)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-6-yl)-3-fluoroazacyclobutan-1-yl]methyl}cyclohexyl]tert-butyl carbamate **48a**

Compound **34c** (122.99 mg, 240 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (65.46 mg, 288.00 μmol) and triethylamine (72.86 mg, 720.00 μmol) were dissolved in methanol (3.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (45.70 mg, 727.20 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **48a** (105 mg, 172.2 μmol, yield: 71.75%) as white solid.

MS m/z (ESI): 610.4 [M+1]

Step 2

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1r,4r)-4-aminocyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **48b**

Compound **48a** (105 mg, 172.2 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **48b** (105 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 510.4 [M+1]

Step 3

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **48**

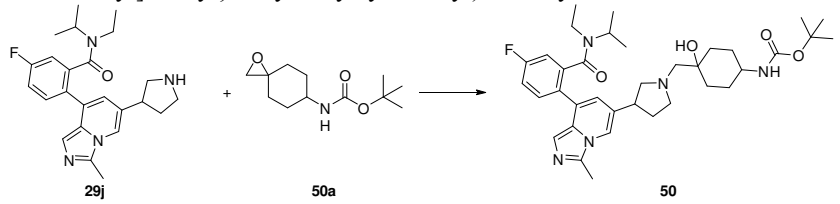
The crude product of Compound **48b** (88 mg) was dissolved in dichloromethane (2.0 mL), followed by the addition of diisopropylethylamine (90.83 mg, 702.77 μmol), cooling to 0°C and the slow dropwise addition of ethanesulfonyl chloride (45.18 mg, 351.38 μmol), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (10 mL), and extracted with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **48** (7.06 mg, 11.73 μmol, yield: 8.35%) as offwhite solid.

MS m/z (ESI): 602.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 – 8.57 (m, 1H), 8.47 (s, 1H), 7.74 – 7.66 (m, 1H), 7.44 – 7.28 (m, 2H), 7.19 (s, 1H), 7.01 – 6.96 (m, 1H), 6.86 – 6.78 (m, 1H), 3.72 – 3.62 (m, 2H), 3.49 – 3.39 (m, 3H), 3.31 – 3.22 (m, 1H), 3.02 – 2.87 (m, 4H), 2.39 – 2.32 (m, 2H), 1.90 – 1.67 (m, 4H), 1.23 – 1.13 (m, 6H), 1.02 – 0.69 (m, 9H), 0.34 – 0.28 (m, 2H).

Example 50

N-(4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl)tert-butyl carbamate **50**



Compound **29j**(200 mg, 382.75 μmol, trifluoroacetate), *N*-{1-oxaspiro[2.5]octan-6-yl}tert-butyl carbamate **50a**(95.70 mg, 421.03 μmol) and triethylamine (193.65 mg, 1.91 mmol) were dissolved in ethanol (1.5 mL), and the mixture was stirred at 70°C for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 7%-37%), to obtain the title Compound **50** (80 mg, 125.8 μmol, yield: 32.9%) as yellow solid.

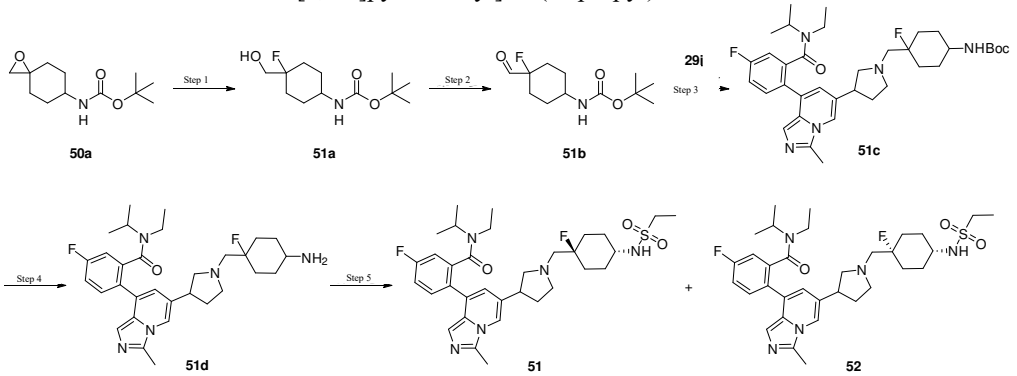
MS m/z (ESI): 636.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 0.16H), 8.03 (s, 1H), 7.70 – 7.60 (m, 1H), 7.44 – 7.28 (m, 2H), 7.04 (s, 1H), 6.83 – 6.62 (m, 2H), 5.21 – 4.53 (m, 1H), 3.67 – 3.41 (m, 4H), 3.27 – 3.08 (m, 4H), 2.96 – 2.82 (m, 1H), 2.60 (s, 3H), 2.36 – 2.21 (m, 1H), 2.17 – 2.01 (m, 1H), 1.77 – 1.44 (m, 7H), 1.43 – 1.29 (m, 12H), 0.99 – 0.65 (m, 7H), 0.32 – 0.20 (m, 2H).

Examples 51 and 52

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-fluorocyclohexyl]methyl}pyrrolidin-3-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **51**

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-fluorocyclohexyl]methyl}pyrrolidin-3-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **52**



Step 1

N-[4-fluoro-4-(hydroxymethyl)cyclohexyl]tert-butyl carbamate **51a**

Compound **50a** (1.0 g, 4.40 mmol) was dissolved in dichloromethane (15.0 mL), and cooled to -78°C under the protection of nitrogen. A hydrogen fluoride pyridine solution (622.88 mg, 4.40 mmol, 5 mL, hydrogen fluoride 70% purity) was added dropwise slowly, and the mixture was stirred at -78°C for 2.0 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to quench the reaction, and the mixture was concentrated under a reduced pressure. The crude product were dissolved in methanol (40 mL), followed by the addition of Boc_2O (4.80 g, 22.00 mmol, 5.05 mL) and DMAP (53.75 mg, 439.95 μmol), and the mixture was stirred at room temperature for 12 hours. Water (30 mL) was added to the mixture, which was then extracted with dichloromethane (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **51a** (450 mg, 1.82 mmol, yield: 41.36%) as white solid.

MS m/z (ESI): 270.1 [M+23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (br d, J = 1.3 Hz, 1H), 3.69 – 3.54 (m, 2H), 3.53 – 3.40 (m, 1H), 2.07 – 1.88 (m, 4H), 1.49 – 1.41 (m, 13H).

Step 2

N-(4-fluoro-4-formylcyclohexyl)tert-butyl carbamate **51b**

Oxalyl chloride (462 mg, 3.64 mmol, 317.53 μL) was dissolved in dichloromethane (5 mL), and the mixture was cooled to -78°C, followed by the dropwise addition of the dichloromethane solution (5 mL) of DMSO (427 mg, 5.47 mmol, 387.83 μL). The mixture was stirred at -78°C for 10 min, followed by the dropwise addition of the solution of Compound **51a**(450 mg, 1.82 mmol) in dichloromethane (5.0 mL). The mixture was stirred at -78°C to allow for reacting for 0.5 hours, triethylamine (1.84 g, 18.20 mmol) was then added, and the mixture was warmed to room temperature and further stirred to allow for reacting for 1 hour. A saturated aqueous ammonium chloride solution (15 mL) was added to quench the reaction, and the reaction mixture was extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **51b** (300 mg, 1.22 mmol, yield: 67.2%) as white solid.

MS m/z (ESI): 286.1 [M+41]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 – 9.69 (m, 1H), 4.56 (br s, 1H), 3.60 – 3.44 (m, 1H), 2.02 – 1.90 (m, 4H), 1.80 – 1.67 (m, 2H), 1.45 (s, 11H).

Step 3

N-(4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)pyrrolidin-1-yl]methyl}-4-fluorocyclohexyl)tert-butyl carbamate **51c**

Compound **29j**(100 mg, 244.79 μmol), Compound **51b**(72 mg, 293.53 μmol) and triethylamine (25 mg, 247.06 μmol) were dissolved in methanol (3.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (47

mg, 747.91 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **51c** (105 mg, 164.63 μmol, yield: 67.25%).
MS m/z (ESI): 638.3 [M+1]

Step 4

2-(6-{1-[(4-amino-1-fluorocyclohexyl)methyl]pyrrolidin-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl) benzamide **51d**

Compound **51c**(100 mg, 156.79 μmol) was dissolved in methane dioxide (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **51d** (100 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 538.2 [M+1]

Step 5

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-fluorocyclohexyl]methyl}pyrrolidin-3-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **51**

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-fluorocyclohexyl]methyl}pyrrolidin-3-yl) imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **52**

The crude product of Compound **51d** (100 mg) and triethylamine (77.63 mg, 767.21 μmol) were dissolved in dichloromethane (3.0 mL), followed by the addition of ethanesulfonyl chloride (39.46 mg, 306.89 μmol), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (C18; mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 33%-63%), to obtain the title Compounds **51** (1.21 mg, 1.92 μmol, yield: 1.25%) and **52** (4.01 mg, 6.37 μmol, yield: 4.15%) both as white solid.

Compound 51:

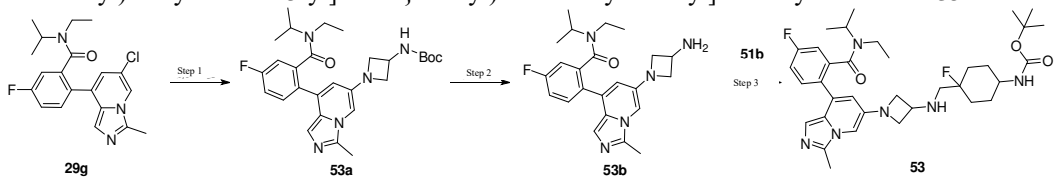
MS m/z (ESI):630.2 [M+1]
HPLC: retention time: 1.101 min.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.70 – 7.60 (m, 1H), 7.42 – 7.25 (m, 2H), 7.04 – 6.96 (m, 2H), 6.73 – 6.61 (m, 1H), 3.46 – 3.42 (m, 1H), 3.28 – 3.24 (m, 2H), 3.03 – 2.89 (m, 4H), 2.78 – 2.61 (m, 5H), 2.57 (s, 3H), 2.21 – 2.11 (m, 1H), 1.91 – 1.62 (m, 7H), 1.51 – 1.39 (m, 2H), 1.22 – 1.13 (m, 3H), 1.09 – 1.01 (m, 2H), 0.93 – 0.75 (m, 6H), 0.34 – 0.25 (m, 2H).

Compound 52:

MS m/z (ESI):630.1 [M+1]
Chiral HPLC: retention time: 0.974 min.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.70 – 7.60 (m, 1H), 7.41 – 7.26 (m, 2H), 7.12 – 6.96 (m, 2H), 6.73 – 6.59 (m, 1H), 3.47 – 3.41 (m, 1H), 3.29 – 3.22 (m, 2H), 3.16 – 3.05 (m, 1H), 3.02 – 2.84 (m, 4H), 2.78 – 2.68 (m, 2H), 2.67 – 2.55 (m, 5H), 2.22 – 2.07 (m, 1H), 1.98 – 1.64 (m, 5H), 1.59 – 1.35 (m, 4H), 1.27 – 1.13 (m, 3H), 1.10 – 0.70 (m, 8H), 0.33 – 0.24 (m, 2H).

Example 53

N-[4-({[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-3-yl]amino}methyl)-4-fluorocyclohexyl]tert-butyl carbamate **53**



Step 1

N-[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-3-yl] tert-butyl carbamate **53a**

Compound **29g** (500 mg, 1.34 mmol), *N*-(azacyclobutan-3-yl)tert-butyl carbamate (276.41 mg, 1.60 mmol) and cesium carbonate (1.31 g, 4.01 mmol) were dissolved in *t*-AmOH (10 mL). Ruphos (124.82 mg, 267.49 μmol) and Pd_2 (dba)$_3$ (122.47 mg, 133.74 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto

allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (25 mL) was added, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **53a** (420 mg, 824.15 μmol, yield: 61.6%) as brown solid.
MS m/z (ESI): 510.1 [M+1]

Step 2

2-[6-(3-aminoazacyclobutan-1-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **53b**

Compound **53a** (200 mg, 392.45 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **53b** (180 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 410.1 [M+1]

Step 3

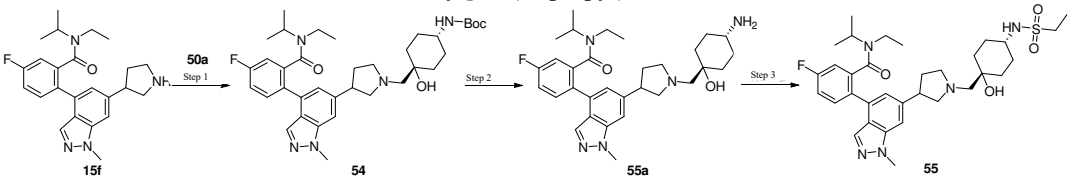
N-[4-({[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-3-yl]amino}methyl)-4-fluorocyclohexyl]tert-butyl carbamate **53**

The crude product of Compound **53b** (160 mg), Compound **51b** (110 mg, 448.45 μmol) and triethylamine (119.00 mg, 1.18 mmol) were dissolved in methanol (3.5 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (73.90 mg, 1.18 mmol) was added, and the reaction mixture was stirred at room temperature for 11 hour. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 5%-35%), to obtain the title Compound **53** (80 mg, 125.24 μmol, yield: 31.95%) as yellow solid.
MS m/z (ESI): 639.7 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (br s, 1H), 7.70 – 7.61 (m, 1H), 7.38 – 7.28 (m, 2H), 6.99 – 6.94 (m, 2H), 6.79 – 6.72 (m, 1H), 6.28 – 6.22 (m, 1H), 3.99 – 3.91 (m, 3H), 3.71 – 3.63 (m, 4H), 3.36 – 3.29 (m, 4H), 2.97 – 2.90 (m, 1H), 2.71 – 2.57 (m, 3H), 1.92 – 1.77 (m, 3H), 1.37 (s, 14H), 0.92 – 0.88 (m, 3H), 0.87 – 0.82 (m, 3H), 0.78 – 0.72 (m, 1H), 0.33 – 0.30 (m, 2H).

Examples 54 and 55

N-[(1*s*,4*s*)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl) pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54**

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55**



Step 1

N-[(1*s*,4*s*)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl) pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54**

Compound **15f** (100 mg, 85.7 μmol), *N*-{1-oxaspiro[2.5]octan-6-yl}tert-butyl carbamate **50a** (19.5 mg, 85.7 μmol) and DIPEA(22.2 mg, 171 μmol) were dissolved in ethanol (1.0 mL), and the mixture was stirred at 60°C for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **54** (30 mg, 47.2 μmol, yield: 55.0 %) as white solid.
MS m/z (ESI): 636.25 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.62 – 7.50 (m, 2H), 7.42 – 7.34 (m, 1H), 7.33 – 7.24 (m, 1H), 7.07 (d, J = 16.0 Hz, 1H), 6.69 (s, 1H), 4.26 – 4.17 (m, 0.19H), 4.03 (d, J = 3.6 Hz, 3H), 3.83 (s, 0.85H), 3.42 – 3.36 (m, 1H), 3.28 – 3.22 (m, 1H), 3.19 – 2.96 (m, 2H), 2.89 – 2.70 (m, 3H), 2.45 – 2.35 (m, 3H), 2.25 – 2.14 (m, 1H), 1.91 – 1.75 (m, 1H), 1.64 – 1.43 (m, 6H), 1.37 (s, 9H), 1.33 – 1.26 (m, 2H), 1.04 – 0.59 (m, 7H), 0.09 (t, J = 6.4 Hz, 2H).

Step 2

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1*s*,4*s*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55a**

Compound **54** (15.0 mg, 23.6 μmol) was dissolved in methane dioxide (0.3 mL), followed by the addition of trifluoroacetic acid (0.1 mL) at 0°C. The mixture was stirred at 0°C to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **55a** (30 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 536.25 [M+1]

Step 3

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55**

The crude product of Compound **55a** (30 mg) and DIPEA(12.2 mg, 94.1 μmol) was dissolved in DMF(0.5 mL), and cooled to 0°C, followed by the addition of ethanesulfonyl chloride (3.02 mg, 23.5 μmol), and the mixture was stirred at room temperature for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 10%-35%), to obtain the title Compound **55** (3.00 mg, 4.78 μmol, yield: 20.3 %) as white solid.
MS m/z (ESI):628.25 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.55 – 7.41 (m, 2H), 7.35 – 7.25 (m, 1H), 7.24 – 7.15 (m, 1H), 6.98 (d, J = 15.6 Hz, 1H), 6.93 – 6.82 (m, 1H), 4.18 – 4.08 (m, 0.27H), 3.94 (s, 3H), 3.01 – 2.56 (m, 9H), 2.37 – 2.24 (m, 3H), 2.19 – 2.06 (m, 1H), 1.79 – 1.70 (m, 1H), 1.67 – 1.40 (m, 6H), 1.32 – 1.21 (m, 2H), 1.16 – 1.05 (m, 3H), 0.94 – 0.48 (m, 7H), 0.08 (t, J = 6.0 Hz, 2H).

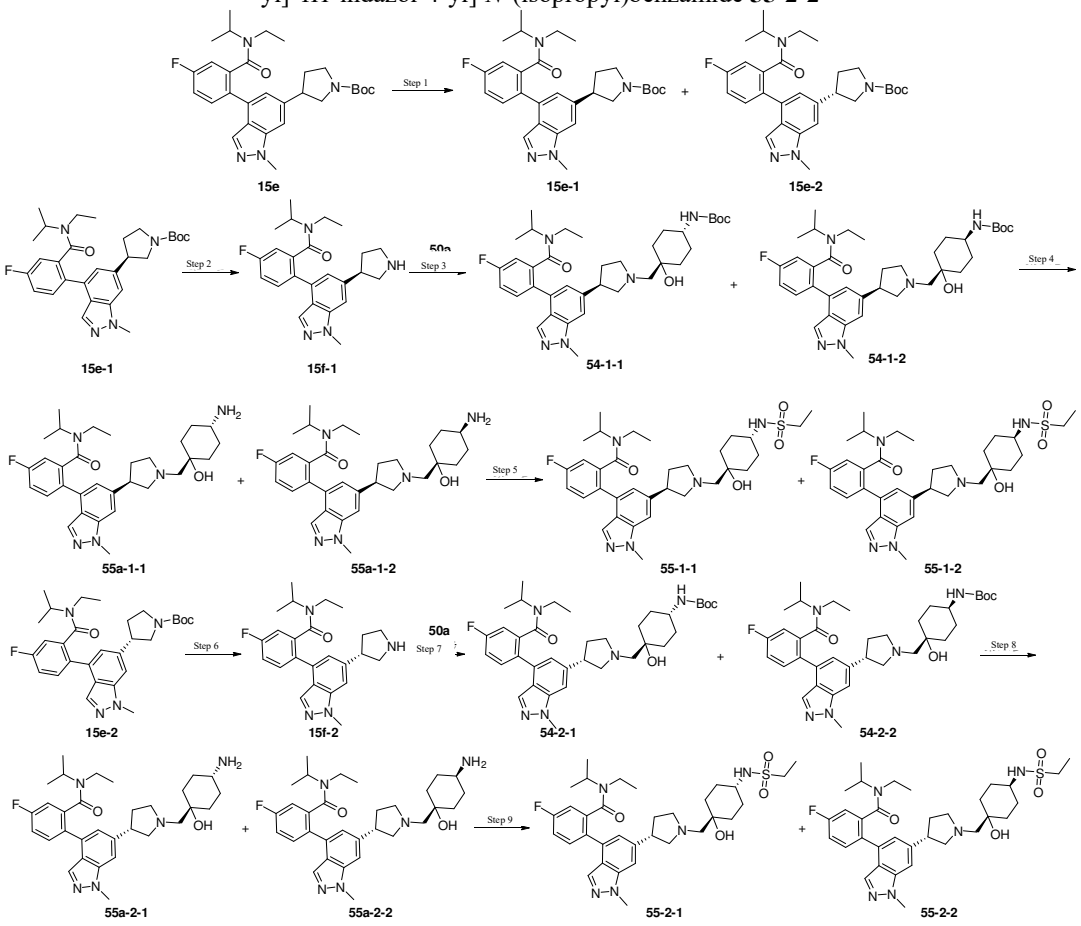
Examples 55-1-1, 55-1-2, 55-2-1 and 55-2-2

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*R*)-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-1-1**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*R*)-1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-1-2**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*S*)-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-2-1**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-2-2**



Step 1

(3*R*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate **15e-1**

(3*S*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate **15e-2**

Compound **15e** (930 mg, 1.83 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL IG (250 mm * 30 mm,10 um), mobile phase: 70% (v/v) carbon dioxide-ethanol (0.1% NH_3)), to obtain the title Compounds **15e-1** (378 mg, 743.2 μmol, yield: 40.65%) and **15e-2** (400 mg, 786.4 μmol, yield: 43.01%).

Single-configuration Compound 15e-1:

MS m/z (ESI):509.2 [M+1]

SFC analysis: retention time: 5.306 min; chromatographic column: DAICEL IG 4.6 mm*250 mm L5 μm; mobile phase: CO_2/MeOH[0.1% NH_3 (7M methanol solution)] = 70/30.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.59 (q, J = 5.6 Hz, 2H), 7.43 – 7.26 (m, 2H), 7.03 (s, 1H), 4.21 (dd, J = 13.6, 7.6 Hz, 0.26H), 4.14 – 3.98 (m, 3H), 3.74 (dd, J = 10.0, 8.0 Hz, 1H), 3.57 – 3.34 (m, 3H), 3.31 – 3.19 (m, 2H), 2.91 – 2.72 (m, 1H), 2.23 (d, J = 5.6 Hz, 1H), 2.12 – 1.97 (m, 1H), 1.41 (d, J = 6.4 Hz, 9H), 1.04 – 0.60 (m, 7H), 0.07 (d, J = 5.6 Hz, 2H).

Single-configuration Compound 15e-2:

MS m/z (ESI):509.2 [M+1]

SFC analysis: retention time: 4.702 min; chromatographic column: DAICEL IG 4.6 mm*250 mm L5 μm; mobile phase: CO_2/MeOH[0.1% NH_3 (7M methanol solution)] = 70/30.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.59 (t, J = 7.2 Hz, 2H), 7.43 – 7.26 (m, 2H), 7.02 (s, 1H), 4.27 – 3.99 (m, 4H), 3.74 (dd, J = 10.0, 8.0 Hz, 1H), 3.44 (dd, J = 54.0, 7.2 Hz, 3H), 3.31 – 3.22 (m, 2H), 2.90 – 2.71 (m, 1H), 2.22 (s, 1H), 2.03 (d, J = 6.8 Hz, 1H), 1.41 (d, J = 6.4 Hz, 9H), 1.05 – 0.57 (m, 7H), 0.07 (d, J = 5.6 Hz, 2H).

Steps 2 and 6

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*R*)-pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **15f-1**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*S*)-pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **15f-2**

At 0°C, Compound **15e-1/15e-2** (110 mg/116 mg, 202.2 μmol/294 μmol) was dissolved in methane dioxide (1.0 mL/4.0 mL), followed by the addition of trifluoroacetic acid (0.3 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **15f-1/15f-2** (200 mg/166 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 15f-1:

MS m/z (ESI): 409.25 [M+1]

Single-configuration Compound 15f-1:

MS m/z (ESI): 409.25 [M+1]

Steps 3 and 7

N-[(1*s*,4*s*)-4-{[(3*R*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54-1-1**

N-[(1*r*,4*r*)-4-{[(3*R*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54-1-2**

N-[(1*s*,4*s*)-4-{[(3*S*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54-2-1**

N-[(1*r*,4*r*)-4-{[(3*S*)-3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **54-2-2**

The crude product of Compound **15f-1/15f-2** (200 mg/166 mg) and DIPEA(111 mg/114 mg, 862 μmol/884 μmol) were dissolved in ethanol (4.0 mL/15.0 mL), followed by the addition of Compound **50a**(49 mg/67 mg, 215 μmol/294 μmol), and the mixture was stirred at 60°C for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the mixture of title Compounds **54-1-1 and 54-1-2/54-2-1 and 54-2-2** (173 mg/350 mg).

Mixture of 54-1-1 and 54-1-2:

MS m/z (ESI):636.35 [M+1]

Mixture of 54-2-1 and 54-2-2:

MS m/z (ESI):636.45 [M+1]

Steps 4 and 8

N-ethyl-5-fluoro-2-{1-methyl-6-[(3*R*)-1-{[(1*s*,4*s*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **55a-1-1**

N-ethyl-5-fluoro-2-{1-methyl-6-[(3*R*)-1-{[(1*r*,4*r*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **55a-1-2**

N-ethyl-5-fluoro-2-{1-methyl-6-[(3*S*)-1-{[(1*s*,4*s*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **55a-2-1**

N-ethyl-5-fluoro-2-{1-methyl-6-[(3*S*)-1-{[(1*r*,4*r*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **55a-2-2**

At 0°C, the mixture of Compounds **54-1-1 and 54-1-2**/the mixture of Compounds **54-2-1 and 54-2-2** (293 mg/187 mg, 322 μmol/294 μmol) was dissolved in methane dioxide (3.0 mL/4.0 mL), followed by the addition of trifluoroacetic acid (0.6 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude mixture of title Compounds **55a-1-1 and 55a-1-2** (210 mg), which was directly used in the next step of reaction without purification. The crude product of the mixture of 55a-2-1 and 55a-2-2 was purified by the HPLC (mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 25%-40%), to obtain the mixture of title Compounds **55a-2-1 and 55a-2-2** (201 mg).

Mixture of 55a-1-1 and 55a-1-2:

MS m/z (ESI): 536.25 [M+1]

Mixture of 55a-2-1 and 55a-2-2:

MS m/z (ESI): 536.10 [M+1]

Steps 5 and 9

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*R*)-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-1-1**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*R*)-1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-1-2**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*S*)-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-2-1**

N-ethyl-5-fluoro-2-[1-methyl-6-[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl]-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **55-1-2**

The crude product of the mixture of Compounds **55a-1-1 and 55a-1-2/the mixture of Compounds 55ª-2-1 and 55a-2-2** (200 mg/160 mg) was dissolved in DMF (2.0 mL/10 mL), followed by the addition of ethanesulfonyl chloride (39.6 mg/38.4 mg, 308 μmol/299 μmol) and DIPEA(159 mg/193, 1.22 mmol/1.49 mmol), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 25%-40%), to obtain the mixture of 55-1-1 and 55-1-2/the mixture of 55-2-1 and 55-2-2 (110 mg/125 mg). The resulting mixture was purified by the preparative SFC (chromatographic column: chiralpak-AD-H, mobile phase: CO_2-MeOH (0.1%NH_3)), to obtain the title Compound **55-1-1/55-1-2** (60.0 mg/4.0 mg, 95.6 μmol/6.37 μmol) and the title Compound **55-2-1/55-2-2** (88.5 mg/7.52 mg, 140 μmol/11 μmol)

Single-configuration Compound 55-1-1:

MS m/z (ESI):628.2 [M+1]

HPLC: retention time: 2.865 min; chromatographic column: Shim-pack Velox C18, 2.7um, 3.0*50 mm; mobile phase: water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid); elution gradient: 5%-95%.

Chiral SFC: retention time: 7.233 min; chromatographic column: DAICEL AD-H 4.6 mm I.D.*250 mm L 5 μm; mobile phase: CO_2/MeOH[0.1% NH_3 (7M methanol solution)] = 60/40.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 1.2 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.40 – 7.35 (m, 1H), 7.32 – 7.25 (m, 1H), 7.07 (d, J = 16.0 Hz, 1H), 6.98 (dd, J = 7.6, 3.2 Hz, 1H), 4.27 – 4.17 (m, 0.21H), 4.08 – 3.96 (m, 3H), 3.89 (s, 1H), 3.42 – 3.33 (m, 2H), 3.27 – 3.21 (m, 1H), 3.05 – 2.91 (m, 4H), 2.90 – 2.69 (m, 4H), 2.44 – 2.36 (m, 2H), 2.27 – 2.14 (m, 1H), 1.89 – 1.77 (m, 1H), 1.68 – 1.50 (m, 6H), 1.43 – 1.30 (m, 2H), 1.22 – 1.14 (m, 3H), 1.05 – 0.59 (m, 7H), 0.08 (t, J = 6.0 Hz, 2H).

Single-configuration Compound 25-1-2:

MS m/z (ESI):628.3 [M+1]

HPLC: retention time: 2.483 min; chromatographic column: Shim-pack Velox C18, 2.7um, 3.0*50 mm; mobile phase: water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid); elution gradient: 5%-95%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 0.97H), 7.79 (s, 1H), 7.62 – 7.47 (m, 2H), 7.43 – 7.33 (m, 1H), 7.29 (t, J = 10.4 Hz, 1H), 7.07 (d, J = 16.0 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 4.25 – 4.17 (m, 0.38H), 4.02 (s, 3H), 3.22 (s, 3H), 3.06 – 2.91 (m, 4H), 2.89 – 2.65 (m, 5H), 2.46 (s, 1H), 2.23 (s, 1H), 1.95 – 1.66 (m, 5H), 1.64 – 1.21 (m, 5H), 1.17 (t, J = 7.2 Hz, 3H), 1.02 – 0.53 (m, 7H), 0.08 (dd, J = 9.6, 6.8 Hz, 2H).

Single-configuration Compound 55-2-1:

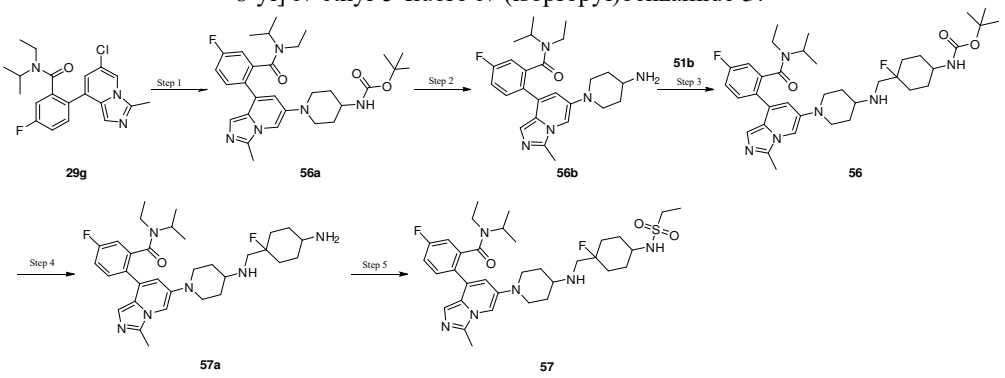
MS m/z (ESI):628.25 [M+1]
HPLC: retention time: 2.877 min; chromatographic column: Shim-pack Velox C18, 2.7um, 3.0*50 mm; mobile phase: water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid); elution gradient: 5%-95%.
Chiral SFC: retention time: 6.242 min; chromatographic column: DAICEL AD-H 4.6 mm I.D.*250 mm L 5 μm; mobile phase: CO_2/MeOH[0.1% NH_3 (7M methanol solution)] = 60/40.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.61 – 7.49 (m, 2H), 7.38 (td, J = 8.4, 2.4 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.11 – 7.03 (m, 1H), 6.98 (dd, J = 7.6, 3.6 Hz, 1H), 4.26 – 4.15 (m, 0.21H), 4.08 – 3.95 (m, 3H), 3.90 (s, 1H), 3.43 – 3.33 (m, 2H), 3.30 – 3.20 (m, 1H), 3.07 – 2.90 (m, 4H), 2.89 – 2.63 (m, 4H), 2.47 – 2.35 (m, 2H), 2.28 – 2.14 (m, 1H), 1.91 – 1.75 (m, 1H), 1.68 – 1.48 (m, 6H), 1.45 – 1.28 (m, 2H), 1.18 (td, J = 7.2, 2.4 Hz, 3H), 1.06 – 0.56 (m, 7H), 0.08 (t, J = 6.0 Hz, 2H).

Single-configuration Compound 55-2-2:
MS m/z (ESI):628.25 [M+1]
HPLC: retention time: 2.874 min; chromatographic column: Shim-pack Velox C18, 2.7um, 3.0*50 mm; mobile phase: water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid); elution gradient: 5%-95%.
Chiral SFC: retention time: 1.985 min; chromatographic column: DAICEL AD-H 4.6 mm I.D.*250 mm L 5 μm; mobile phase: CO_2/MeOH[0.1% NH_3 (7M methanol solution)] = 60/40.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.64 – 7.55 (m, 2H), 7.40 (td, J = 8.4, 2.4 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.13 – 7.04 (m, 1H), 6.95 (d, J = 6.8 Hz, 1H), 4.72 (brs, 1H), 4.19 (dt, J = 14.0, 7.2 Hz, 0.28H), 4.11 – 3.98 (m, 3H), 3.77 – 3.34 (m, 4H), 3.30 – 3.21 (m, 3H), 3.19 – 2.72 (m, 6H), 2.37 – 2.29 (m, 1H), 2.14 – 1.94 (m, 1H), 1.88 – 1.65 (m, 4H), 1.53 – 1.37 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H), 1.01 – 0.57 (m, 7H), 0.08 (t, J = 6.0 Hz, 2H).

Examples 56 and 57

N-[4-({[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperidin-4-yl]amino}methyl)-4-fluorocyclohexyl]tert-butyl carbamate **56**

2-[6-(4-{[(4-ethanesulfonamido-1-fluorocyclohexyl)methyl]amino}piperidin-1-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **57**



Step 1

N-[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperidin-4-yl]tert-butyl carbamate **56a**

Compound **29g** (300 mg, 802.46 μmol), *N*-(piperidin-4-yl)tert-butyl carbamate (321.43 mg, 1.60 mmol) and cesium carbonate (784.37 mg, 2.41 mmol) were dissolved in tert-amyl alcohol (5 mL). Ruphos (74.89 mg, 160.49 μmol) and Pd_2 (dba)$_3$ (73.48 mg, 80.25 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **56a** (400 mg, 743.95 μmol, yield: 92.71%).
MS m/z (ESI): 538.2 [M+1]

Step 2

2-[6-(4-aminopiperidin-1-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **56b**

Compound **56a** (250.00 mg, 325.48 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **56b** (200 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 438.1 [M+1]

Step 3

N-[4-({[1-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperidin-4-yl]amino}methyl)-4-fluorocyclohexyl]tert-butyl carbamate **56**

The crude product of Compound **56b** (135 mg, 244.75 μmol, trifluoroacetate), Compound **51b**(68 mg, 277.22 μmol) and triethylamine (74 mg, 731.30 μmol) were dissolved in methanol (3.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (47 mg, 747.91 μmol) was added, and the mixture was stirred at room temperature for 2.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 41%-71%), to obtain the title Compound **56** (6.19 mg, 9.28 μmol, yield: 3.79%).

MS m/z (ESI): 667.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.63 (m, 1H), 7.41 – 7.22 (m, 3H), 7.00 – 6.93 (m, 1H), 6.81 – 6.70 (m, 1H), 6.64 – 6.56 (m, 1H), 3.51 – 3.40 (m, 3H), 3.29 – 3.23 (m, 1H), 3.01 – 2.58 (m, 6H), 2.54 (s, 3H), 1.96 – 1.83 (m, 4H), 1.72 – 1.55 (m, 3H), 1.45 – 1.32 (m, 15H), 0.98 – 0.68 (m, 7H), 0.36 – 0.29 (m, 2H).

Step 4

2-[6-(4-{[(4-amino-1-fluorocyclohexyl)methyl]amino}piperidin-1-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl) benzamide **57a**

Compound **56** (150.00 mg, 224.94 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **57a** (130 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 567.2 [M+1]

Step 5

2-[6-(4-{[(4-ethanesulfonamido-1-fluorocyclohexyl)methyl]amino}piperidin-1-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **57**

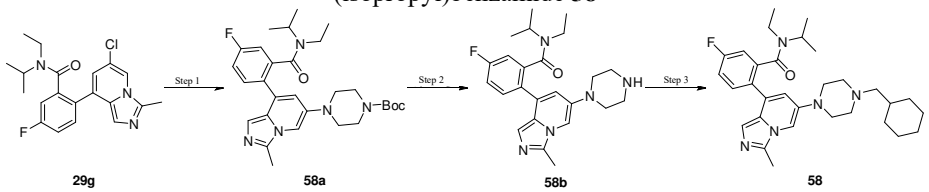
The crude product of Compound **57a** (120 mg, 211.74 μmol, trifluoroacetate) and triethylamine (108 mg, 1.07 mmol) were dissolved in dichloromethane (2.0 mL), followed by the addition of ethanesulfonyl chloride (33 mg, 256.65 μmol), and the mixture was stirred at room temperature for 0.25 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (C18; mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 26%-56%), to obtain the title Compound **57** (13.21 mg, 20.05 μmol, yield: 9.47 %) as yellow solid.

MS m/z (ESI):659.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.63 (m, 1H), 7.40 – 7.22 (m, 3H), 7.08 (d, J = 8.0 Hz, 1H), 6.99 – 6.93 (m, 1H), 6.63 – 6.56 (m, 1H), 3.50 – 3.37 (m, 3H), 3.32 – 3.27 (m, 1H), 3.15 – 3.04 (m, 1H), 3.03 – 2.87 (m, 3H), 2.86 – 2.57 (m, 5H), 2.54 (s, 3H), 1.95 – 1.81 (m, 4H), 1.78 – 1.67 (m, 2H), 1.58 – 1.45 (m, 4H), 1.42 – 1.31 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 1.11 – 0.71 (m, 7H), 0.35 – 0.29 (m, 2H).

Example 58

2-{6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-methylimidazo[1,5-*a*]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **58**



Step 1

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **58a**

Compound **29g** (500 mg, 1.34 mmol), piperazin-1-tert-butyl carboxylate (498.20 mg, 2.67 mmol) and cesium carbonate (1.31 g, 4.01 mmol) were dissolved in tert-amyl alcohol (10 mL). Ruphos (124.82 mg, 267.49 μmol) and Pd_2 (dba)$_3$ (122.47 mg, 133.74 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (25 mL) was added, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with saturated brine (25 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution

system, to obtain the title Compound **58a** (660 mg, 1.26 mmol, yield: 94.24%).
MS m/z (ESI): 524.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.61 (m, 1H), 7.43 – 7.27 (m, 3H), 7.01 – 6.94 (m, 1H), 6.60 (s, 1H), 3.49 – 3.37 (m, 5H), 3.31 – 3.28 (m, 1H), 2.92 (s, 5H), 2.55 (s, 3H), 1.42 (s, 9H), 1.11 – 0.72 (m, 7H), 0.36 – 0.27 (m, 2H).

Step 2

N-ethyl-5-fluoro-2-[3-methyl-6-(piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **58b**

Compound **58a** (50.00 mg, 95.49 μmol) was dissolved in methane dioxide (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 18%-48%), to obtain the title Compound **58b** (1.36 mg, 3.21 μmol, yield: 3.36%).
MS m/z (ESI): 424.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.62 (m, 1H), 7.41 – 7.19 (m, 3H), 7.00 – 6.93 (m, 1H), 6.63 – 6.56 (m, 1H), 3.48 – 3.43 (m, 2H), 3.35 – 3.29 (m, 2H), 2.99 – 2.91 (m, 4H), 2.83 (br s, 4H), 2.58 – 2.52 (m, 3H), 1.09 – 0.72 (m, 7H), 0.34 – 0.28 (m, 2H).

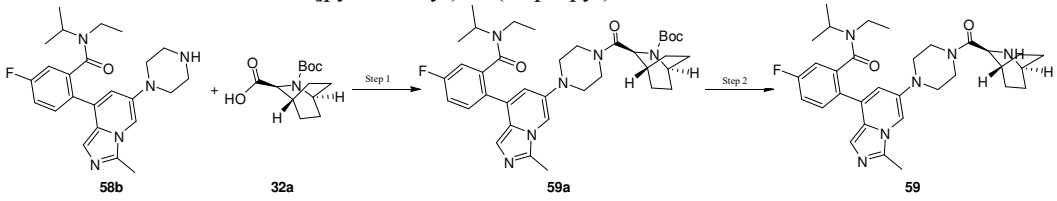
Step 3

2-{6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-methylimidazo[1,5-*a*]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **58**

The crude product of Compound **58b** (129.01 mg, 240 μmol, trifluoroacetate), cyclohexane formaldehyde (33 mg, 294.20 μmol) and triethylamine (50 mg, 494.12 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (46 mg, 732 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 60%-90%), to obtain the title Compound **58** (48.8 mg, 93.9 μmol, yield: 39.13 %).
MS m/z (ESI): 520.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.64 (m, 1H), 7.41 – 7.24 (m, 3H), 7.00 – 6.93 (m, 1H), 6.64 – 6.57 (m, 1H), 3.48 – 3.40 (m, 1H), 3.31 – 3.26 (m, 1H), 3.09 – 2.87 (m, 5H), 2.54 (s, 3H), 2.48 – 2.40 (m, 4H), 2.16 – 2.10 (m, 2H), 1.78 – 1.62 (m, 5H), 1.57 – 1.45 (m, 1H), 1.25 – 1.08 (m, 4H), 0.91 – 0.72 (m, 8H), 0.35 – 0.28 (m, 2H).

Example 59

N-ethyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **59**



Step 1

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **59a**

(1*R*,3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.2]octan-3-carboxylic acid **32a**(68 mg, 266.34 μmol) and *N,N*-diisopropylethylamine (157 mg, 1.21 mmol, 211.59 μL) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (62 mg, 323.42 μmol), HOBT (50 mg, 370.03 μmol) and Compound **58b** (130 mg, 241.84 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **59a** (100 mg, 151.3 μmol, yield: 62.6%).
MS m/z (ESI): 661.2 [M+1]

Step 2

N-ethyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **59**

Compound **59a** (100 mg, 151.33 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL).

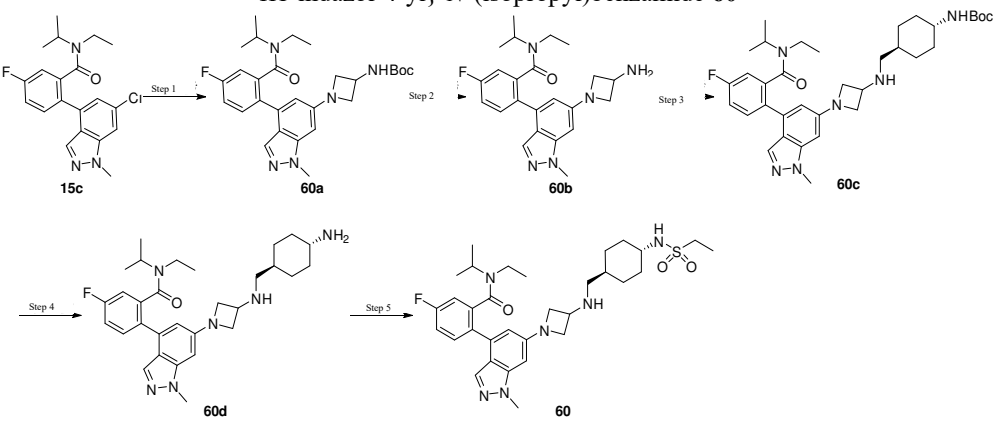
The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-56%), to obtain the title Compound **59** (37.9 mg, 67.6 μmol, yield: 44.7%) as yellow solid.

MS m/z (ESI): 561.6 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.63 (m, 1H), 7.41 – 7.29 (m, 3H), 7.00 – 6.95 (m, 1H), 6.64 – 6.58 (m, 1H), 3.91 (s, 1H), 3.75 – 3.49 (m, 4H), 3.48 – 3.40 (m, 1H), 3.09 – 2.74 (m, 7H), 2.55 (s, 3H), 1.84 – 1.40 (m, 9H), 1.12 – 0.73 (m, 7H), 0.34 – 0.27 (m, 2H).

Example 60

N-ethyl-5-fluoro-2-{1-methyl-6-[3-({[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}amino)azacyclobutan-1-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **60**



Step 1

N-[1-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-3-yl]tert-butyl carbamate **60a**

Compound **15c** (143 mg, 267 μmol) and *N*-(azacyclobutan-3-yl)tert-butyl carbamate (46.1 mg, 267 μmol) were dissolved in toluene (0.9 mL) and tertiary butanol (0.3 mL). $Pd(Oac)_2$ (6.01 mg, 26.7 μmol), Xphos(25.5 mg, 53.5 μmol) and sodium tert-butoxide (38.6 mg, 401 μmol) were added, and the mixture was stirred at 100°C under a nitrogen atmosphere to allow for reacting for 8.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **60a** (90 mg, 177 μmol, yield: 66.0%) as white solid.

MS m/z (ESI): 510.25 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 – 7.51 (m, 3H), 7.37 (td, J = 8.8, 2.8 Hz, 1H), 7.26 (dd, J = 9.2, 2.8 Hz, 1H), 6.41 (s, 1H), 6.33 (d, J = 1.6 Hz, 1H), 4.44 – 4.19 (m, 1H), 4.14 – 4.06 (m, 2H), 3.91 (d, J = 3.6 Hz, 3H), 3.64 (t, J = 6.4 Hz, 2H), 3.42 – 3.34 (m, 1H), 3.29 – 3.21 (m, 2H), 1.40 (s, 9H), 0.94 – 0.63 (m, 7H), 0.16 (d, J = 6.4 Hz, 2H).

Step 2

2-[6-(3-aminoazacyclobutan-1-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **60b**

Compound **60a** (85.0 mg, 167 μmol) was dissolved in methane dioxide (1.0 mL), followed by the addition of trifluoroacetic acid (0.2 mL) at 0°C. The mixture was stirred at 0°C to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **60b** (110 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 410.2 [M+1]

Step 3

N-[(1*r*,4*r*)-4-({[1-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-3-yl]amino}methyl)cyclohexyl]tert-butyl carbamate **60c**

The crude product of Compound **60a** (110 mg) and *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (37.9 mg, 167 μmol) were dissolved in dichloromethane (1.0 mL). Sodium triacetoxyborohydride (106 mg, 500 μmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **60c** (30.0 mg, 103 μmol, yield: 28.9%) as yellow solid.

MS m/z (ESI): 621.30 [M+1]

Step 4

N-ethyl-5-fluoro-2-{1-methyl-6-[3-({[(1*r*,4*r*)-4-aminocyclohexyl]methyl}amino)azacyclobutan-1-yl]-1*H*-indazol-

4-yl}-*N*-(isopropyl)benzamide **60d**

Compound **60c** (25.0 mg, 40.3 μmol) was dissolved in methane dioxide (0.2 mL), followed by the addition of trifluoroacetic acid (0.05 mL) at 0°C. The mixture was stirred at 0°C to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **60d** (50 mg), which was directly used in the next step of reaction without purification.

MS m/z (ESI): 521.25 [M+1]

Step 5

N-ethyl-5-fluoro-2-{1-methyl-6-[3-({[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}amino)azacyclobutan-1-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **60**

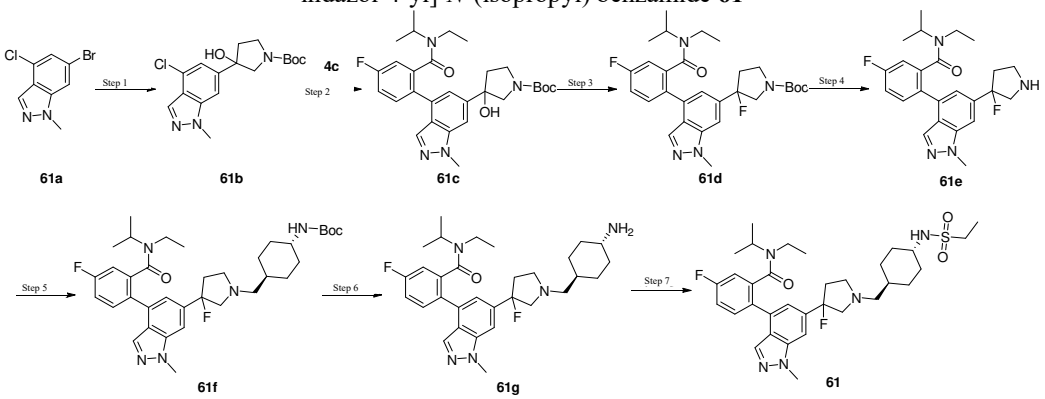
The crude product of Compound **60d** (50 mg) and diisopropylethylamine ((20.8 mg, 161 μmol) were dissolved in DMF(0.5 mL), followed by the addition of the solution of ethanesulfonyl chloride (5.19 mg, 40.3 μmol) in DMF(0.2 mL), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (C18; mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 10%-35%), to obtain the title Compound **60** (3.0 mg, 4.90 μmol, yield: 12.1%) as white solid.

MS m/z (ESI): 613.25 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 – 7.37 (m, 2H), 7.22 (td, J = 8.8, 2.8 Hz, 1H), 7.13 (td, J = 8.8, 2.8 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.30 – 6.12 (m, 2H), 4.14 – 4.06 (m, 0.27H), 3.89 (q, J = 6.8 Hz, 2H), 3.76 (d, J = 3.6 Hz, 3H), 3.51 (dq, J = 12.8, 6.4 Hz, 1H), 3.35 (d, J = 6.4 Hz, 2H), 2.86 – 2.78 (m, 3H), 2.75 – 2.66 (m, 1H), 2.17 (d, J = 6.8 Hz, 2H), 1.72 (d, J = 10.4 Hz, 2H), 1.63 (d, J = 15.2 Hz, 2H), 1.21 – 0.99 (m, 7H), 0.96 – 0.86 (m, 1H), 0.84 – 0.68 (m, 5H), 0.65 – 0.51 (m, 3.72H), 0.01 (d, J = 6.4 Hz, 2.33H).

Example 61

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl) benzamide **61**



Step 1

3-(4-chloro-1-methyl-1H-indazol-6-yl)-3-hydroxylpyrrolidin-1-tert-butyl carboxylate **61b**

6-Bromo-4-chloro-1-methylindazole **61a** (1.80 g, 7.33 mmol) was dissolved in THF(36 mL), to which isopropylmagnesium chloride (2M, 7.80 mL) was dropwise added at 0°C, followed by reacting for 2 hours at 50°C. The above mixture was cooled to 0°C, followed by the addition of the solution of 3-oxopyrrolidin-1-tert-butyl carboxylate (4.08 g, 22.02 mmol) in THF(4.0 mL), and the resulting mixture was allowed to react at 22°C for 12 hours. The reaction mixture was quenched with water (100 mL), extracted with ethyl acetate (100.0 mL × 3), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system. to obtain the crude product of title Compound **61b** (3.15 g, 8.95 mmol, yield: 122%) as yellow solid.

MS m/z (ESI): 352.2 [M+1]

Step 2

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-hydroxylpyrrolidin-1-tert-butyl carboxylate **61c**

Compound **61b** (1.6 g, 3.18 mmol) and Compound **4c**(1.68 g, 3.50 mmol) were dissolved in dioxane (60 mL) and water (10 mL). Sodium carbonate (675 mg, 6.37 mmol) and Pd(dppf)Cl_2 (233 mg, 318 μmol) were added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 6.0 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **61c** (470 mg, 896 μmol, yield: 28.1%) as yellow solid.

MS m/z (ESI): 525.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.73 (m, 2H), 7.59 (m, 1H), 7.43 – 7.26 (m, 2H), 7.24 – 7.17 (m, 1H), 5.57 (d, J = 10.4 Hz, 1H), 4.27 – 4.18 (m, 0.19H), 4.06 (s, 3H), 3.65 – 3.34 (m, 5H), 3.26 – 3.12 (m, 1H), 2.85 (m, 1H), 2.39 – 2.23 (m, 1H), 2.08 – 2.00 (m, 1H), 1.41 (dd, J = 13.2, 4.8 Hz, 10H), 1.03 – 0.80 (m, 4H), 0.67 (m, 3H), 0.11 (d, J = 6.0 Hz, 2H).

Step 3

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-fluoropyrrolidin-1-tert-butyl carboxylate **61d**

Compound **61c** (200 mg, 381.2 μmol) was dissolved in dichloromethane (4.0 mL), and cooled to -78°C, followed by the dropwise addition of the solution of DAST (73.74 mg, 457.47 μmol) in dichloromethane (1 mL). The mixture was stirred at -45°C to allow for reacting for 2.0 hour. The reaction mixture was quenched by adding water (10 mL), and extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **61d** (199 mg, 378 μmol, yield: 99%) as yellow solid.
MS m/z (ESI): 527.2 [M+1]

Step 4

N-ethyl-5-fluoro-2-[6-(3-fluoropyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **61e**

Compound **61d** (110 mg, 208 μmol) was dissolved in methane dioxide (4.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **61e** (135 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 427.2 [M+1]

Step 5

N-[(1r,4r)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-fluoropyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **61f**

The crude product of Compound **61e** (135 mg) and *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (47.4 mg, 208 μmol) were dissolved in dichloromethane (10.0 mL), and stirred at room temperature for 0.5 hours. The reaction mixture was cooled to 0°C, followed by adding sodium triacetoxyborohydride (221 mg, 1.04 mmol) and stirring at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **61f** (90 mg, 141 μmol, yield: 67.5%) as yellow solid.
MS m/z (ESI): 638.2 [M+1]

Step 6

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **61g**

Compound **61f** (90 mg, 141 μmol) was dissolved in methane dioxide (4.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **61g** (102 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 538.1 [M+1]

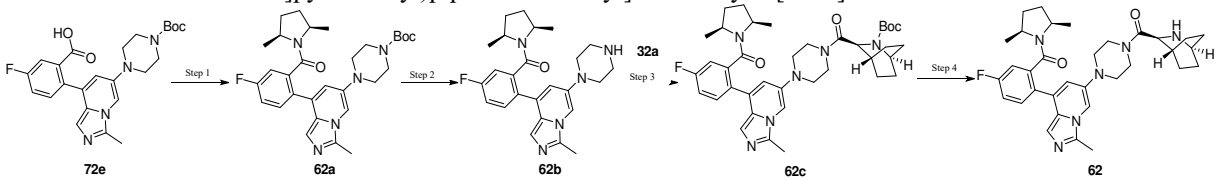
Step 7

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **61**

The crude product of Compound **61g** (102 mg) and DIPEA (182 mg, 1.41 mmol) were dissolved in DMF(5.0 mL), and cooled to 0°C. Ethanesulfonyl chloride (18.1 mg, 141 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 25%-40%), to obtain the title Compound **61** (39.8 mg, 63.1 μmol, yield: 43.2 %) as white solid.
MS m/z (ESI):630.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 5.2 Hz, 1H), 7.70 (s, 1H), 7.64 – 7.56 (m, 1H), 7.40 (td, J = 8.4, 2.4 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.13 (s, 1H), 7.05 – 6.94 (m, 1H), 4.26 – 4.18 (m, 0.20H), 4.08 (d, J = 4.0 Hz, 3H), 3.43 – 3.37 (m, 1H), 3.26 – 3.19 (m, 1H), 3.14 – 2.79 (m, 7H), 2.73 – 2.69 (m, 0.80H), 2.40 – 2.36 (m, 1H), 2.34 – 2.25 (m, 3H), 1.90 – 1.83 (m, 2H), 1.82 – 1.76 (m, 1H), 1.60 – 1.12 (m, 7H), 1.07 – 0.59 (m, 9H), 0.13 (t, J = 6.4 Hz, 2H).

Example 62

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperazin-1-carbyl]-2-azabicyclo[2.2.2]octane **62**



Step 1

4-(8-{2-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **62a**

(2*R*,5*S*)-2,5-dimethylpyrrolidine (39.39 mg, 290.43 μmol, hydrochloride) and Compound **72e** (120 mg, 264.03 μmol) were dissolved in DMF (2.0 mL). DIPEA (102.37 mg, 792.09 μmol), EDCI (75.92 mg, 396.05 μmol) and HOBt (53.51 mg, 396.05 μmol) were added, and the mixture was stirred at room temperature to allow for reacting for 12.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **62a** (110 mg, 205.36 μmol, yield: 77.8%).

MS m/z (ESI): 536.4 [M+1]

Step 2

1-(8-{2-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazine **62b**

Compound **62a** (110 mg, 205.36 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **62b** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 436.2 [M+1]

Step 3

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **62c**

Compound **32a**(44 mg, 172.34 μmol) and *N,N*-diisopropylethylamine (64 mg, 495.19 μmol) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (48 mg, 250.39 μmol), HOBT (33 mg, 244.22 μmol) and Compound **62b** (90 mg, 163.77 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **62c** (80 mg, 118.90 μmol, yield: 72.60%).

MS m/z (ESI): 673.3 [M+1]

Step 4

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperazin-1-carbyl]-2-azabicyclo[2.2.2]octane **62**

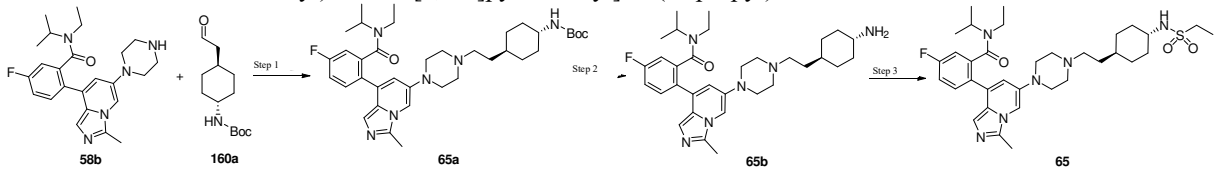
Compound **62c** (80 mg, 118.9 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (13.56 mg, 118.90 μmol). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **62** (4.01 mg, 7.00 μmol, yield: 5.89%).

MS m/z (ESI): 573.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.80 – 7.74 (m, 1H), 7.37 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.18 (s, 1H), 6.87 – 6.81 (m, 1H), 4.56 – 4.54 (m, 1H), 3.72 – 3.65 (m, 3H), 3.57 – 3.46 (m, 3H), 3.19 – 3.08 (m, 4H), 2.66 (s, 3H), 2.23 – 2.18 (m, 2H), 2.06 – 2.03 (m, 2H), 1.88 – 1.84 (m, 2H), 1.63 – 1.56 (m, 4H), 1.37 – 1.32 (m, 7H), 0.92 – 0.88 (m, 3H).

Example 65

N-ethyl-5-fluoro-2-[3-methyl-6-(4-{2-[(1*r*,4*r*) -4-ethanesulfonamidocyclohexyl]ethyl}piperazine -1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **65**



Step 1

N-[(1*r*,4*r*)-4-{2-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-yl]ethyl}cyclohexyl]tert-butyl carbamate **65**[a]

Compound **58b** (102.13 mg, 190 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-(2-oxoethyl)cyclohexyl]tert-butyl carbamate **160a** (55.02 mg, 228.00 μmol) and triethylamine (19.23 mg, 190.00 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (35.82 mg, 570.00 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **65a** (70 mg, 107.88 μmol, yield: 56.78%) as brown oil.

MS m/z (ESI): 649.2 [M+1]

Step 2

N-ethyl-5-fluoro-2-[3-methyl-6-(4-{2-[(1*r*,4*r*)-4-aminocyclohexyl]ethyl}piperazine -1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **65b**

Compound **65a** (75 mg, 115.59 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 30 min. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **65b** (70 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 549.2 [M+1]

Step 3

N-ethyl-5-fluoro-2-[3-methyl-6-(4-{2-[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]ethyl}piperazine -1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **65**

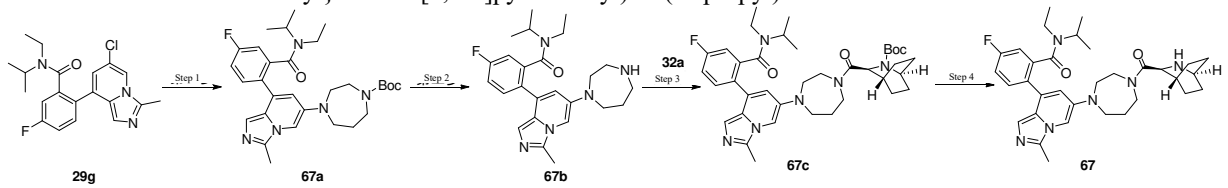
The crude product of Compound **65b** (70 mg) was dissolved in dichloromethane (2.0 mL), followed by the addition of triethylamine (58.48 mg, 577.95 μmol), cooling to 0°C and the slow dropwise addition of ethanesulfonyl chloride (29.72 mg, 231.18 μmol), and the mixture was stirred at room temperature for 30 min. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **65** (13.48 mg, 21.03 μmol, yield: 18.20%).

MS m/z (ESI): 641.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.63 (m, 1H), 7.41 – 7.20 (m, 3H), 7.03 – 6.94 (m, 2H), 6.64 – 6.58 (m, 1H), 3.51 – 3.39 (m, 1H), 3.30 – 3.23 (m, 1H), 3.06 – 2.87 (m, 8H), 2.55 (s, 3H), 2.48 (s, 4H), 2.33 (t, J=7.3 Hz, 2H), 1.91 – 1.80 (m, 2H), 1.79 – 1.65 (m, 2H), 1.40 – 1.30 (m, 2H), 1.22 – 1.15 (m, 5H), 1.04 – 0.70 (m, 10H), 0.32 (d, J=6.6 Hz, 2H).

Example 67

N-ethyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,4-diazacycloheptan-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **67**



Step 1

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-1,4-diazacycloheptan-1-tert-butyl carboxylate **67a**

Compound **29g** (300 mg, 802.5 μmol), 1,4-diazacycloheptan-1-tert-butyl carboxylate (321.43 mg, 1.60 mmol) and cesium carbonate (784.37 mg, 2.41 mmol) were dissolved in tert-amyl alcohol (8.0 mL). Ruphos (74.89 mg, 160.49 μmol) and Pd_2 (dba)$_3$ (73.48 mg, 80.25 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (25 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **67a** (379 mg, 704.90 μmol, yield: 87.84%).

MS m/z (ESI): 538.3 [M+1]

Step 2

2-[6-(1,4-diazacycloheptan-1-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **67b**

Compound **67a** (120.00 mg, 223.19 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1.0 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **67b** (101 mg).

MS m/z (ESI): 438.2 [M+1]

Step 3

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-1,4-diazacycloheptan-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **67c**

Compound **32a**(49.72 mg, 194.76 μmol) and *N,N*-diisopropylethylamine (160.17 mg, 1.24 mmol, 215.87 μL) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (51.25 mg, 267.35 μmol), HOBT (36.60 mg, 270.89 μmol) and Compound **67b** (97.66 mg, 177.05 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.5% ammonia water), elution gradient: 37%-67%), to obtain the title Compound **67c** (79 mg, 117.06 μmol, yield: 66.12 %).

MS m/z (ESI): 675.3 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,4-diazacycloheptan-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **67**

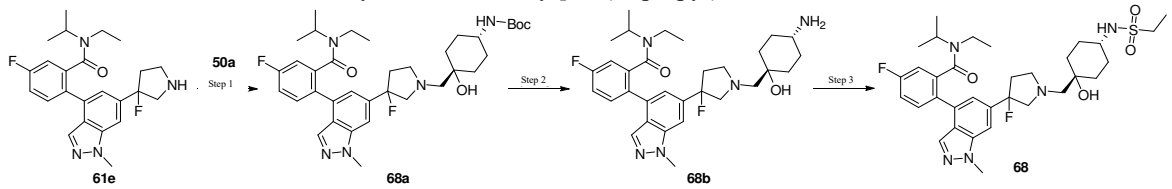
Compound **67c** (55 mg, 81.5 μmol) was dissolved in methane dioxide (1.5 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title Compound **67** (0.34 mg, yield: 0.7%).

MS m/z (ESI): 575.5 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.72 – 7.58 (m, 1H), 7.21 – 6.97 (m, 4H), 6.76 – 6.63 (m, 1H), 4.01 – 3.76 (m, 3H), 3.60 – 3.32 (m, 10H), 3.00 – 2.86 (m, 3H), 2.83 – 2.71 (m, 1H), 2.33 – 2.26 (m, 1H), 1.93 – 1.72 (m, 5H), 1.53 – 1.49 (m, 1H), 1.24 – 1.18 (m, 2H), 0.90 – 0.79 (m, 7H), 0.25 – 0.16 (m, 2H).

Example 68

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **68**



Step 1

N-[(1*s*,4*s*)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl) -3-fluoropyrrolidin-1-yl]methyl}-4-hydroxylcyclohexyl]tert-butyl carbamate **68a**

Compound **61e** (60.0 mg, 141 μmol), *N*-{1-oxaspiro[2.5]octan-6-yl}tert-butyl carbamate **50a**(44.8 mg, 197 μmol) and DIPEA(36.4 mg, 281 μmol, 49.0 μL) were dissolved in ethanol (3.0 mL), and the mixture was stirred at 60°C for 6.0 hours. Compound **50a** (44.8 mg, 197 μmol) was supplemented, and the mixture was stirred at 60°C for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **68a** (56.7 mg, 86.7 μmol, yield: 61.6%) as yellow solid.

MS m/z (ESI): 654.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 3.6 Hz, 1H), 7.70 (s, 1H), 7.60 (m, 1H), 7.43 – 7.25 (m, 2H), 7.15 (s, 1H), 6.69 (s, 1H), 4.22 (s, 0.26H), 4.08 (d, J = 4.0 Hz, 3H), 3.86 (s, 1H), 3.44 – 3.34 (m, 1H), 3.25 – 3.10 (m, 3H), 3.02 (s, 1H), 2.97 – 2.78 (m, 2H), 2.48 – 2.35 (m, 3H), 2.26 (s, 1H), 1.64 – 1.43 (m, 6H), 1.42 – 1.30 (m, 11H), 1.01 (d, J = 14.4 Hz, 1H), 0.87 (d, J = 6.8 Hz, 3H), 0.67 (m, 3H), 0.17 – 0.09 (m, 2H).

Step 2

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*s*,4*s*)-4-amino-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **68b**

Compound **68a** (50.0 mg, 76.5 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.4 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **68b** (40 mg), which was directly used in the next step of reaction without purification.
MS m/z (ESI): 554.1 [M+1]

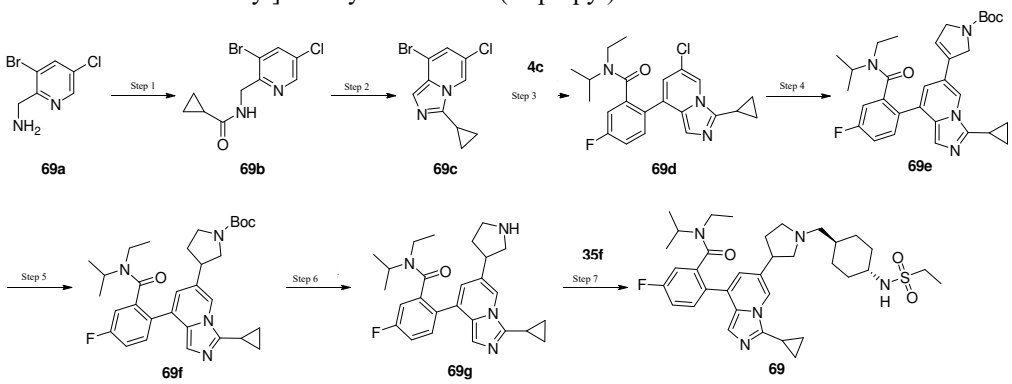
Step 3

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*s*,4*s*)-4-ethanesulfonamido-1-hydroxylcyclohexyl]methyl}pyrrolidin-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **68**

The crude product of Compound **68b** (40 mg) and DIPEA(37.4 mg, 289 μmol, 50.3 μL) were dissolved in DMF(2.0 mL), and cooled to 0°C, followed by the addition of ethanesulfonyl chloride (11.2 mg, 86.7 μmol), and the mixture was stirred at room temperature for 1.0 hour. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 5%-30%), to obtain the title Compound **68** (13.2 mg, 20.4 μmol, yield: 26.4%) as white solid.
MS m/z (ESI):646.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 4.0 Hz, 1H), 7.69 (s, 1H), 7.60 (dt, J = 10.4, 5.2 Hz, 1H), 7.44 – 7.27 (m, 2H), 7.14 (s, 1H), 6.99 (dd, J = 7.6, 4.0 Hz, 1H), 4.22 (s, 0.22H), 4.08 (d, J = 4.0 Hz, 3H), 3.93 (s, 1H), 3.39 (dd, J = 11.6, 5.2 Hz, 1H), 3.27 – 3.12 (m, 3H), 3.07 – 2.79 (m, 6H), 2.45 (d, J = 8.4 Hz, 2H), 2.27 (d, J = 7.6 Hz, 1H), 1.59 (s, 6H), 1.34 (d, J = 7.2 Hz, 2H), 1.18 (d, J = 2.8 Hz, 3H), 1.00 (s, 0.65H), 0.87 (d, J = 6.8 Hz, 2.67H), 0.74 – 0.61 (m, 4H), 0.15 – 0.08 (m, 2H).

Example 69

2-[3-cyclopropyl-6-(1-{[(1r,4r) -4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **69**



Step 1

N-[(3-bromo-5-chloropyridin-2-yl)methyl]cyclopropane formamide **69b**

(3-Bromo-5-chloropyridin-2-yl)methylamine **69a** (1 g, 3.88 mmol, hydrochloride) was dissolved in dichloromethane (7.0 mL), and cooled to 0°C, followed by the addition of cyclopropanecarboxylic acid (267.00 mg, 3.10 mmol), triethylamine (1.18 g, 11.63 mmol, 1.62 mL) and HATU (1.77 g, 4.65 mmol). The mixture was stirred at room temperature to allow for reacting for 12.0 hour. Water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **69b** (1.0 g, 3.45 mmol, yield: 89.1%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 291.0 [M+1]

Step 2

8-bromo-6-chloro-3-cyclopropylimidazo[1,5-*a*]pyridine **69c**

Compound **69b** (1 g, 3.45 mmol) was dissolved in toluene (58 mL), followed by the addition of $POCl_3$ (5.30 g, 34.54 mmol, 3.22 mL). The mixture was stirred at 100°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. A 10% aqueous sodium hydroxide solution (100 mL) was added to regulate the mixture to alkalinity, and the mixture was then extracted with dichloromethane (50 mL x 2). The organic phases were combined, washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **69c** (498 mg, 1.83 mmol, yield: 53.1%).
MS m/z (ESI): 273.0 [M+1]

Step 3

2-{6-chloro-3-cyclopropylimidazo[1,5-a]pyridin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **69d**

Compound **69c** (200 mg, 736.54 μmol), Compound **4c**(370.35 mg, 1.10 mmol) and sodium carbonate (234.19 mg, 2.21 mmol) were dissolved in dioxane (3.0 mL) and water (1.0 mL). Pd (dppf)Cl_2 (53.89 mg, 73.65 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **69d** (254 mg, 635.18 μmol, yield: 86.24%).

MS m/z (ESI): 400.2 [M+1]

Step 4

3-(3-cyclopropyl-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **69e**

Compound **69d** (250 mg, 625.18 μmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (276.81 mg, 937.76 μmol) and cesium carbonate (611.08 mg, 1.88 mmol) were dissolved in dioxane (6.0 mL) and water (1.0 mL). Pd(dtbpf)Cl_2 (40.75 mg, 62.52 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **69e** (198 mg, 371.73 μmol, yield: 59.46%).

Step 5

3-(3-cyclopropyl-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **69f**

Compound **69e** (198 mg, 371.73 μmol) was dissolved in tetrahydrofuran (5.0 mL), followed by the addition of Pd/C (45.15 mg, 371.73 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 3.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **69f** (198 mg, 370.33 μmol, yield: 99.6%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 535.4 [M+1]

Step 6

2-[3-cyclopropyl-6-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **69g**

The crude product of Compound **69f** (198.00 mg, 370.33 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (42.23 mg, 370.33 μmol, 28.53 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **69g** (168 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 435.3 [M+1]

Step 7

2-[3-cyclopropyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **69**

The crude product of Compound **69g** (158 mg, 363.60 μmol) and Compound **35f**(273.06 mg, 727.19 μmol) were dissolved in acetonitrile (10.0 mL), followed by the addition of potassium carbonate (251.26 mg, 1.82 mmol), and the mixture was stirred at room temperature for 0.5 hours. TBAI (13.43 mg, 36.36 μmol) was added, and the mixture was further stirred at room temperature for 1.0 hour. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 6%-36%), to obtain the title Compound **69** (92 mg, 144.23 μmol, yield: 39.67 %).

MS m/z (ESI): 638.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 – 9.90 (m, 1H), 8.51 – 8.43 (m, 1H), 7.67 – 7.60 (m, 1H), 7.58 – 7.51 (m, 1H), 7.47 – 7.37 (m, 2H), 7.08 – 6.98 (m, 2H), 3.82 – 3.71 (m, 2H), 3.59 – 3.52 (m, 1H), 3.48 – 3.40 (m, 1H), 3.37 – 3.29 (m, 1H), 3.24 – 3.17 (m, 1H), 3.15 – 3.07 (m, 2H), 3.01 – 2.94 (m, 3H), 2.61 – 2.53 (m, 1H), 2.43 – 2.32 (m, 1H), 1.94 – 1.72 (m, 5H), 1.68 – 1.54 (m, 1H), 1.31 – 1.15 (m, 9H), 1.14 – 1.01 (m, 5H), 0.96 – 0.89 (m, 3H), 0.84 – 0.77 (m, 1H), 0.72 – 0.63 (m, 2H), 0.44 – 0.27 (m, 2H).

Example 70

2-[6-(4-{2-[4-(5,6-dimethoxypyridazin-3-yl)phenyl]ethyl}piperazin-1-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-

ethyl-5-fluoro-*N*-(isopropyl)benzamide **70**

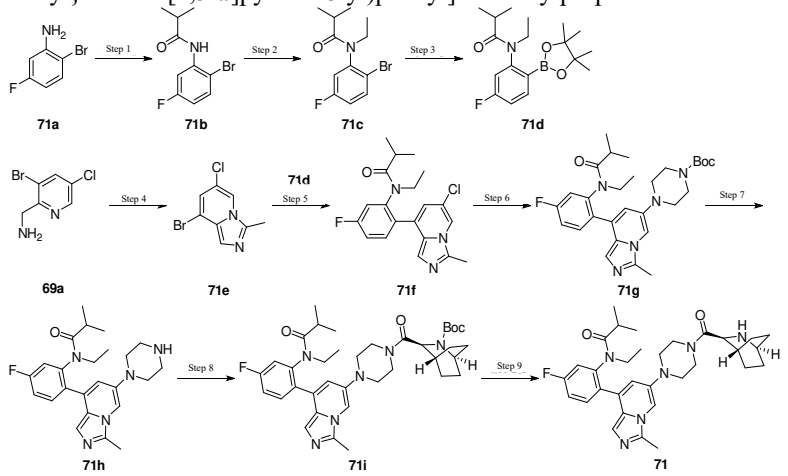
Compound **58b** (49.09 mg, 104.54 μmol, trifluoroacetate) and triethylamine (35.26 mg, 348.47 μmol) were dissolved in methanol (0.5 mL), and the mixture was stirred at room temperature for 0.25 hours. The methanol solution (0.1 mL) of Compound **42c** (30 mg, 116.16 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (14.60 mg, 232.31 μmol) was added, and the mixture was stirred at room temperature for 0.5 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 34%-64%), to obtain the title Compound **70** (6.25 mg, 9.39 μmol, yield: 8.08%) as yellow solid.

MS m/z (ESI): 666.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H), 7.65 (t, J = 5.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.22 – 7.10 (m, 4H), 6.97 – 6.92 (m, 1H), 6.79 (s, 1H), 4.24 (s, 3H), 4.02 (s, 3H), 3.58 – 3.37 (m, 2H), 3.25 – 3.15 (m, 2H), 3.15 – 3.04 (m, 2H), 3.03 – 2.96 (m, 1H), 2.95 – 2.89 (m, 2H), 2.76 – 2.71 (m, 4H), 2.66 – 2.61 (m, 3H), 1.38 – 1.22 (m, 1H), 1.20 – 1.11 (m, 1H), 1.01 (t, J = 7.0 Hz, 3H), 0.95 – 0.87 (m, J = 6.8 Hz, 3H), 0.79 (t, J = 7.0 Hz, 1H), 0.28 (d, J = 6.4 Hz, 2H).

Example 71

N-ethyl-*N*-[5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)phenyl]-2-methylpropionamide **71**



Step 1

N-(2-bromo-5-fluorophenyl)-2-methylpropionamide **71b**

2-Bromo-5-fluoroaniline **71a** (5 g, 26.31 mmol) and triethylamine (5.33 g, 52.63 mmol) were dissolved in dichloromethane (50 mL), and cooled to 0°C, followed by the dropwise addition of 2-methylpropionyl chloride (3.5 g, 32.85 mmol, 3.44 mL). The mixture was stirred at room temperature to allow for reacting for 12.0 hour. The reaction mixture was washed with water (35 mL x 3), and then washed with a 1N aqueous HCl solution (35 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **71b** (5.0 g, 19.22 mmol, yield: 73.05%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 262.2 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 2.9, 11.1 Hz, 1H), 7.75 (br s, 1H), 7.48 (dd, J = 5.8, 8.9 Hz, 1H), 6.72 (ddd, J = 3.1, 7.6, 8.8 Hz, 1H), 2.61 (td, J = 7.0, 13.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H).

Step 2

N-(2-bromo-5-fluorophenyl)-*N*-ethyl-2-methylpropionamide **71c**

Compound **71b** (2 g, 7.69 mmol) was dissolved in tetrahydrofuran (20 mL), and cooled to 0°C under a nitrogen atmosphere, followed by the addition of NaH (615.08 mg, 15.38 mmol, 60% purity), and the mixture was stirred to allow for reacting for 0.5 hours. At 0°C, iodoethane (2.40 g, 15.38 mmol, 1.24 mL) was added dropwise, and the

mixture was slowly warmed to room temperature and stirred to allow for reacting for 12 hours. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (20 mL), and extracted with ethyl acetate (30 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **71c** (1.8 g, 6.25 mmol, yield: 81.24%) as white solid.
MS m/z (ESI): 289.8 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 5.8, 8.7 Hz, 1H), 7.09 – 6.95 (m, 2H), 4.06 (qd, J = 7.1, 13.9 Hz, 1H), 3.33 (qd, J = 7.1, 13.9 Hz, 1H), 2.20 (td, J = 6.7, 13.4 Hz, 1H), 1.16 – 1.07 (m, 6H), 1.01 (d, J = 6.8 Hz, 3H).

Step 3

N-ethyl-*N*-[5-fluoro-2-(tetramethyl-1,3,2-dioxaboran-2-yl)phenyl]-2-methylpropionamide **71d**

Compound **71c** (1.6 g, 5.55 mmol), potassium acetate (2.72 g, 27.76 mmol) and bis(pinacolato)diboron (2.82 g, 11.11 mmol) were dissolved in DMAc (20 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (609.43 mg, 832.88 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 12 hours. After the mixture was cooled to room temperature, 20 mL of water was added, and the mixture was extracted with ethyl acetate (30ml × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **71d** (1.2 g, 3.58 mmol, yield: 64.47%) as yellow solid.
MS m/z (ESI): 336.0 [M+1]

Step 4

8-bromo-6-chloro-3-methylimidazo[1,5-a]pyridine **71e**

Compound **69a** (5.0 g, 19.38 mmol, hydrochloride) was dissolved in acetic anhydride (50 mL), followed by the addition of p-toluenesulfonic acid (3.34 g, 19.38 mmol). The mixture was stirred at 100°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding a 10% aqueous sodium hydroxide solution (150 mL). The mixture was filtered, and the filter cake was dried under vacuum to obtain the crude product of title Compound **71e** (5.35 g, 21.79 mmol, yield: 112.4%).
MS m/z (ESI): 246.8 [M+1]

Step 5

N-(2-{6-chloro-3-methylimidazo[1,5-a]pyridin-8-yl}-5-fluorophenyl)-*N*-ethyl-2-methylpropionamide **71f**

Compound **71e** (400 mg, 1.63 mmol), Compound **71d** (546.18 mg, 1.63 mmol) and sodium carbonate (518.07 mg, 4.89 mmol) were dissolved in dioxane (5 mL) and water (1.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (119.22 mg, 162.93 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **71f** (280 mg, 748.96 μmol, yield: 45.97%).
MS m/z (ESI): 374.2 [M+1]

Step 6

4-{8-[2-(*N*-ethyl-2-methylpropionamido)-4-fluorophenyl]-3-methylimidazo[1,5-*a*]pyridin-6-yl}piperazin-1-tert-butyl carboxylate **71g**

Compound **71f** (280.00 mg, 748.96 μmol), piperazin-1-tert-butyl carboxylate (280 mg, 1.50 mmol) and cesium carbonate (733 mg, 2.25 mmol) were dissolved in tert-amyl alcohol (3 mL). Ruphos (70 mg, 150.01 μmol) and $Pd_2(dba)_3$ (70 mg, 76.44 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **71g** (400 mg, 763.88 μmol, yield: 101.99%) as yellow solid.
MS m/z (ESI): 524.2 [M+1]

Step 7

N-ethyl-*N*-{5-fluoro-2-[3-methyl-6-(piperazin-1-yl)imidazo[1,5-a]pyridin-8-yl]phenyl}-2-methylpropionamide **71h**

Compound **71g** (150 mg, 286.46 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **71h** (120 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 424.2 [M+1]

Step 8

(1*R*,3*S*,4*S*)-3-(4-{8-[2-(*N*-ethyl-2-methylpropionamido)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-

yl}piperazin-1-carbonyl)-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **71i**

Compound **32a** (61 mg, 238.93 μmol) and *N,N*-diisopropylethylamine (87 mg, 673.15 μmol, 117.25 μL) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (65 mg, 339.07 μmol), HOBT (45 mg, 333.03 μmol) and Compound **71h** (120 mg, 223.24 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **71i** (80 mg, 121.06 μmol, yield: 54.23%).

MS m/z (ESI): 661.6 [M+1]

Step 9

N-ethyl-*N*-[5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)phenyl]-2-methylpropionamide **71**

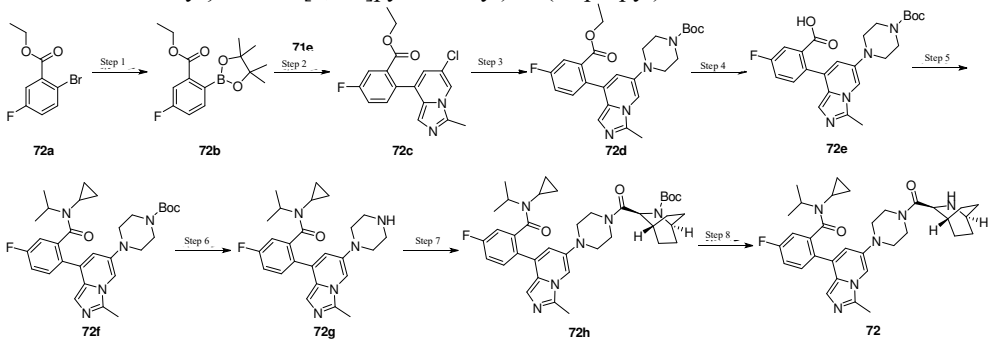
Compound **71i** (80 mg, 121.06 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 20%-50%), to obtain the title Compound **71** (24.22 mg, 43.2 μmol, yield: 35.68 %) as yellow solid.

MS m/z (ESI): 561.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 – 7.52 (m, 1H), 7.48 – 7.13 (m, 3H), 6.83 (s, 1H), 6.56 – 6.47 (m, 1H), 3.94 (s, 1H), 3.89 – 3.77 (m, 1H), 3.71 – 3.52 (m, 4H), 3.12 – 2.93 (m, 4H), 2.91 – 2.76 (m, 2H), 2.55 (s, 3H), 2.42 – 2.28 (m, 1H), 1.86 – 1.37 (m, 9H), 1.22 – 0.68 (m, 7H), 0.59 – 0.53 (m, 2H).

Example 72

N-cyclopropyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **72**



Step 1

5-fluoro-2-(tetramethyl-1,3,2-dioxaboran-2-yl)ethyl benzoate **72b**

2-Bromo-5-ethyl fluorobenzoate **72a** (20 g, 80.95 mmol), potassium acetate (12.0 g, 122.47 mmol) and bis(pinacolato)diboron (31.0 g, 122.1 mmol) were dissolved in dioxane (200 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (6.00 g, 8.20 mmol) was added, and the mixture was stirred at 100°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and then filtered, and the filtrate was concentrated under a reduced pressure . The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the crude product of title Compound **72b** (32.4 g, 110.16 mmol, yield: 136.1%) as yellow oil. The crude product was directly used in the next step of reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 1H), 7.51 – 7.45 (m, 1H), 7.25 – 7.19 (m, 1H), 4.44 – 4.35 (m, 2H), 1.42 (s, 12H), 1.41 – 1.37 (m, 3H).

Step 2

2-{6-chloro-3-methylimidazo[1,5-a]pyridin-8-yl}-5-ethyl fluorobenzoate **72c**

Compound **71e** (2 g, 8.15 mmol), Compound **72b**(2.93 g, 8.48 mmol) and sodium carbonate (2.59 g, 24.44 mmol) were dissolved in dioxane (18 mL) and water (3.0 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (600 mg, 820.00 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **72c** (1.23 g, 3.70 mmol, yield: 45.37%).

MS m/z (ESI): 333.2 [M+1]

Step 3

4-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-*a*]pyridin-6-yl}piperazin-1-tert-butyl carboxylate **72d**

Compound **72c** (1.23 g, 3.70 mmol), piperazin-1-tert-butyl carboxylate (1.38 g, 7.39 mmol) and cesium carbonate (3.61 g, 11.09 mmol) were dissolved in tert-amyl alcohol (15 mL). Ruphos (345 mg, 739.34 μmol) and Pd_2 (dba)$_3$ (340 mg, 371.29 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **72d** (1.0 g, 2.07 mmol, yield: 56.1%).

MS m/z (ESI): 483.4 [M+1]

Step 4

2-(6-{4-[(tert-butoxy)carbonyl]piperazin-1-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoic acid **72e**

Compound **72d** (1.0 g, 2.07 mmol) was dissolved in methanol (2.0 mL), tetrahydrofuran (10 mL) and water (2.0 mL), followed by the addition of LiOH.H_2O (260.89 mg, 6.22 mmol), and the mixture was stirred at 40°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and regulated to pH = 7-8 with 1N aq. HCl, and the organic solvent was removed under a reduced pressure. The aqueous phase was further regulated to pH = 1 with 1N aq. HCl, and extracted with ethyl acetate (30 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The title Compound **72e** (650 mg, 1.43 mmol, yield: 69.0%) was obtained.

MS m/z (ESI): 455.0 [M+1]

Step 5

4-(8-{2-[cyclopropyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **72f**

Isopropylcyclopropylamine (50 mg, 368.64 μmol, hydrochloride) and Compound **72e**(120 mg, 264.03 μmol) were dissolved in DMAc (2.0 mL). DIPEA (170 mg, 1.32 mmol, 229.11 μL) and HATU (151 mg, 397.13 μmol) were added, and the mixture was stirred at 60°C allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **72f** (110 mg, 205.36 μmol, yield: 77.8%).

MS m/z (ESI): 536.4 [M+1]

Step 6

N-cyclopropyl-5-fluoro-2-[3-methyl-6-(piperazin-1-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **72g**

Compound **72f** (110 mg, 205.36 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **72g** (120 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 436.2 [M+1]

Step 7

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[cyclopropyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **72h**

Compound **32a**(61 mg, 238.93 μmol) and *N,N*-diisopropylethylamine (142 mg, 1.10 mmol, 191.37 μL) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (63 mg, 328.64 μmol), HOBT (45 mg, 333.03 μmol) and Compound **72g** (120 mg, 218.36 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **72h** (80 mg, 118.90 μmol, yield: 54.45 %).

MS m/z (ESI): 673.5 [M+1]

Step 8

N-cyclopropyl-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **72**

Compound **72h** (80 mg, 118.9 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 21%-51%), to obtain the title Compound **72** (8.69 mg, 15.17 μmol, yield: 12.76 %) as yellow solid.

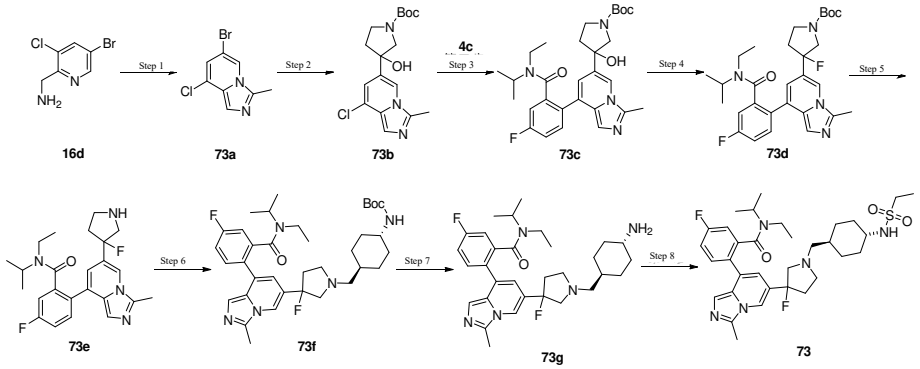
MS m/z (ESI): 573.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 – 7.60 (m, 1H), 7.42 – 7.24 (m, 3H), 7.03 (s, 1H), 6.55 (s, 1H), 4.25 – 4.09

(m, 1H), 3.96 (s, 1H), 3.80 – 3.51 (m, 5H), 3.14 – 2.93 (m, 4H), 2.86 (s, 1H), 2.53 (s, 3H), 1.86 – 1.39 (m, 10H), 1.11 – 0.83 (m, 5H), 0.62 – 0.13 (m, 4H).

Example 73

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-N-(isopropyl) benzamide **73**



Step 1

6-bromo-8-chloro-3-methylimidazo[1,5-a]pyridine **73a**

Compound **16d** (10.0 g, 45.15 mmol) was dissolved in acetic anhydride (100 mL), followed by the addition of p-toluenesulfonic acid (4.0 g, 23.23 mmol). The mixture was stirred at 100°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. Dichloromethane (40 mL) was added for dilution, and the mixture was regulated to PH = 8 with a saturated aqueous sodium carbonate solution. The mixture was extracted with dichloromethane (60 mL x 3), and the organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure . The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **73a** (8.0 g, 32.6 mmol, yield: 72.2%).

MS m/z (ESI): 246.7 [M+1]

Step 2

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-3-hydroxylpyrrolidin-1-tert-butyl carboxylate **73b**

Compound **73a** (1.5 g, 6.11 mmol) was dissolved in tetrahydrofuran (15 mL), and cooled to 0°C, followed by the addition of the solution of *i*-PrMgCl.LiCl in tetrahydrofuran (1.3 M, 7.05 mL). The mixture was stirred at 0°C to allow for reacting for 10 min, and 3-oxopyrrolidin-1-tert-butyl carboxylate (1.51 g, 8.81 mmol) was then added. The mixture was stirred at room temperature to allow for reacting for 2.0 hour. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (30 mL), and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **73b** (650 mg, 1.85 mmol, yield: 30.24%) as brown solid.

MS m/z (ESI): 352.2 [M+1]

Step 3

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-3-hydroxylpyrrolidin-1-tert-butyl carboxylate **73c**

Compound **73b** (650 mg, 1.85 mmol) and Compound **4c**(1 g, 2.98 mmol) were dissolved in dioxane (9.0 mL) and water (1.5 mL). Potassium phosphate (984.33 mg, 4.64 mmol) and Pd (dtbpf)Cl_2 (124.02 mg, 190.29 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 95°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **73c** (388 mg, 739.58 μmol, yield: 40.0 %).

MS m/z (ESI): 525.3 [M+1]

Step 4

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-3-fluoropyrrolidin-1-tert-butyl carboxylate **73d**

Compound **73c** (330 mg, 629.02 μmol) was dissolved in dichloromethane (4.0 mL), and cooled to -60°C, followed by the dropwise addition of DAST(202.78 mg, 1.26 mmol). The mixture was stirred -60°C to allow for reacting for

1.0 hour, and then slowly warmed to room temperature, at which the mixture was stirred to allow for reacting for 1.0 hour. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (20 mL), and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **73d** (305 mg, 579.17 μmol, yield: 92.07%) was obtained.
MS m/z (ESI): 527.1 [M+1]

Step 5

N-ethyl-5-fluoro-2-[6-(3-fluoropyrrolidin-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **73e**

Compound **73d** (100 mg, 189.89 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **73e** (90 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 427.3 [M+1]

Step 6

N-[(1*r*,4*r*)-4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-3-fluoropyrrolidin-1-yl]methyl}cyclohexyl]tert-butyl carbamate **73f**

The crude product of Compound **73e** (90 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (45.42 mg, 199.81 μmol) and triethylamine (50.55 mg, 499.52 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (31.70 mg, 504.51 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **73f** (108 mg, 169.33 μmol, yield: 101.7%).
MS m/z (ESI): 638.3 [M+1]

Step 7

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1r,4r)-4-aminocyclohexyl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **73g**

Compound **73f** (106 mg, 166.5 μmol) was dissolved in dichloromethane (1.9 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **73g** (95 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 538.3 [M+1]

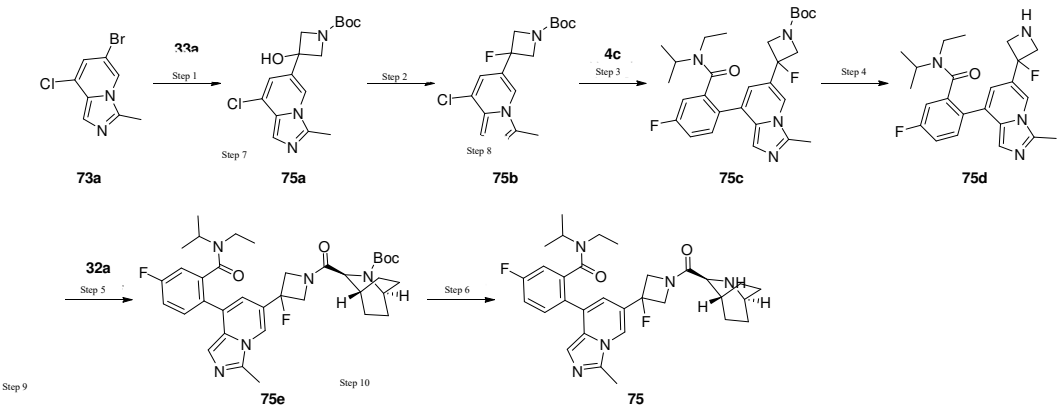
Step 8

N-ethyl-5-fluoro-2-[6-(3-fluoro-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-N-(isopropyl) benzamide **73**

The crude product of Compound **73g** (89.53 mg, 137.38 μmol, TF) and DIPEA (88.77 mg, 686.89 μmol, 119.64 μL) was dissolved in dichloromethane (2.0 mL), and cooled to 0°C, followed by the addition of ethanesulfonyl chloride (44.16 mg, 343.44 μmol), and the mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture. The mixture was extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 3%-33%), to obtain the title Compound **73** (8.91 mg, 14.15 μmol, yield: 10.3%) as yellow solid.
MS m/z (ESI): 630.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.05 – 7.99 (m, 1H), 7.72 – 7.65 (m, 1H), 7.43 – 7.30 (m, 2H), 7.11 – 6.97 (m, 2H), 6.67 – 6.61 (m, 1H), 3.50 – 3.46 (m, 1H), 3.31 – 3.26 (m, 1H), 3.03 – 2.89 (m, 6H), 2.70 – 2.62 (m, 4H), 2.36 – 2.26 (m, 3H), 1.93 – 1.76 (m, 4H), 1.41 – 0.72 (m, 16H), 0.37 – 0.29 (m, 2H).

Example 75

N-ethyl-5-fluoro-2-(6-{3-fluoro-1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl) benzamide **75**



Step 1

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-3-hydroxyazacyclobutan-1-tert-butyl carboxylate **75a**

Compound **73a** (1 g, 4.07 mmol) was dissolved in tetrahydrofuran (20 mL), and cooled to 0°C, followed by the addition of the solution of *i*-PrMgCl.LiCl in tetrahydrofuran (1.3 M, 4.70 mL). The mixture was stirred at 0°C to allow for reacting for 20 min, followed by the dropwise addition of the solution of 3-oxoazacyclobutan-1-tert-butyl carboxylate **33a** (836.78 mg, 4.89 mmol) in tetrahydrofuran (2.0 mL). The mixture was stirred at 0°C to allow for reacting for 2.0 hours. The reaction mixture was quenched by adding water (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **75a** (650 mg, 1.92 mmol, yield: 47.24%).

MS m/z (ESI): 338.0 [M+1]

Step 2

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-3-fluoroazacyclobutan-1-tert-butyl carboxylate **75b**

Compound **75a** (100 mg, 296.03 μmol) was dissolved in dichloromethane (3.0 mL), and cooled to 0°C, followed by the dropwise addition of DAST(95.43 mg, 592.07 μmol, 78.22 μL). The mixture was stirred at room temperature to allow for reacting for 12 hour. The reaction mixture was quenched by adding water (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the crude product of title Compound **75b** (150 mg, 441.45 μmol, yield: 149.12%).

MS m/z (ESI): 339.9 [M+1]

Step 3

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-3-fluoroazacyclobutan-1-tert-butyl carboxylate **75c**

The crude product of Compound **75b** (150 mg, 441.45 μmol), Compound **4c**(221.97 mg, 662.17 μmol) and cesium carbonate (431.50 mg, 1.32 mmol) were dissolved in dioxane (3.0 mL) and water (1.0 mL). $Pd(dtbpf)Cl_2$ (28.77 mg, 44.14 μmol) was added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **75c** (170 mg, 331.65 μmol, yield: 75.1 %).

MS m/z (ESI): 513.3 [M+1]

Step 4

N-ethyl-5-fluoro-2-[6-(3-fluoroazacyclobutan-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **75d**

Compound **75c** (170 mg, 331.65 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **75d** (170 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 413.2 [M+1]

Step 5

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]- 4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-3-fluoroazacyclobutan-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **75e**

Compound **32a** (105.22 mg, 412.15 μmol), *N,N*-diisopropylethylamine (159.80 mg, 1.24 mmol, 215.36 μL), EDCI(118.51 mg, 618.22 μmol) and HOBt (83.53 mg, 618.22 μmol) were dissolved in dichloromethane (3 mL).

The mixture was stirred at room temperature for 0.5 hours, followed by the addition of the crude product of Compound **75d** (170 mg), and the mixture was then stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **75e** (100 mg, 153.9 μmol, yield: 37.3%).
MS m/z (ESI): 650.4 [M+1]

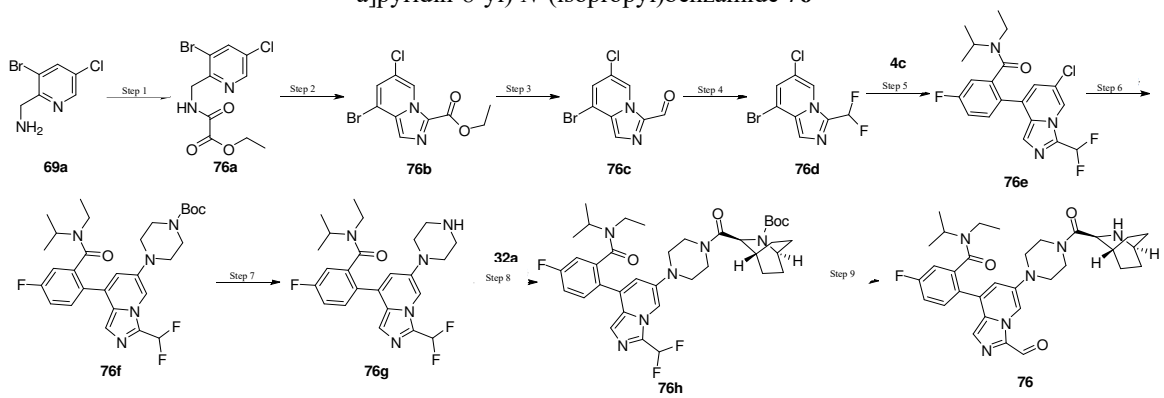
Step 6

N-ethyl-5-fluoro-2-(6-{3-fluoro-1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl) benzamide **75**

Compound **75e** (100 mg, 153.9 μmol) was dissolved in methane dioxide (3.5 mL), followed by the addition of trifluoroacetic acid (17.55 mg, 153.90 μmol, 11.86 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 25%-55%), to obtain the title Compound **75** (50 mg, 90.97 μmol, yield: 59.1 %) as white solid.
MS m/z (ESI): 550.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.74 – 7.64 (m, 1H), 7.46 – 7.30 (m, 2H), 7.16 – 7.06 (m, 1H), 6.71 – 6.59 (m, 1H), 4.99 – 4.44 (m, 3H), 4.41 – 4.15 (m, 1H), 3.74 – 3.66 (m, 1H), 3.53 – 3.44 (m, 1H), 3.00 – 2.85 (m, 1H), 2.82 – 2.74 (m, 1H), 2.66 (s, 3H), 1.92 – 1.30 (m, 10H), 0.93 (d, J = 6.8 Hz, 3H), 0.81 – 0.69 (m, 3H), 0.42 – 0.31 (m, 2H).

Example 76

N-ethyl-5-fluoro-2-(3-formyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **76**



Step 1

{[(3-bromo-5-chloropyridin-2-yl)methyl]aminoformyl}ethyl formate **76a**

Compound **69a** (10.94 g, 49.39 mmol) and triethylamine (10.00 g, 98.79 mmol) were dissolved in dichloromethane (60 mL), and cooled to 0°C, followed by the slow dropwise addition of 2-chloro-2-oxoethyl acetate (6.74 g, 49.39 mmol, 5.52 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **76a** (21.05 g, 65.47 mmol, yield: 132.5%) as white solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 322.8 [M+1]

Step 2

8-bromo-6-chloroimidazo[1,5-a]pyridin-3-ethyl carboxylate **76b**

The crude product of Compound **76a** (21.05 g, 65.47 mmol) was dissolved in toluene (100 mL), followed by the addition of phosphorus oxychloride (70.26 g, 458.26 mmol, 41.95 mL). The mixture was stirred at 110°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. A saturated aqueous sodium bicarbonate solution (100 mL) was added, and the reaction mixture was then extracted with ethyl acetate (60 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **76b** (3.6 g, 11.86 mmol, yield: 18.12%) as yellow solid.
MS m/z (ESI): 304.9[M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 – 9.27 (m, 1H), 7.66 (d, J = 0.7 Hz, 1H), 7.21 (d, J = 1.4 Hz, 1H), 4.45 (q, J = 7.1

Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

Step 3

8-bromo-6-chloroimidazo[1,5-a]pyridin-3-formaldehyde **76c**

Compound **76b** (1.2 g, 3.95 mmol) was dissolved in dichloromethane (20 mL). Under a nitrogen atmosphere, the mixture was cooled to -78°C, followed by the slow dropwise addition of DIBALH(1.0M, 7.91 mL), and the mixture was stirred at -78°C to allow for reacting for 2.0 hours. The reaction mixture was diluted by adding dichloromethane (50 mL), and the quenched by adding water (50 ml). The organic layer was washed with water (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **76c** (640 mg, 2.47 mmol, yield: 62.39%).

MS m/z (ESI): 260.8 [M+1]

Step 4

8-bromo-6-chloro-3-(difluoromethyl)imidazo[1,5-a]pyridine **76d**

Compound **76c** (640 mg, 2.47 mmol) was dissolved in dichloromethane (10 mL), and cooled to 0°C, followed by the slow dropwise addition of DAST (1.19 g, 7.40 mmol, 977.60 μL). The mixture was stirred at room temperature to allow for reacting for 12.0 hour. A saturated aqueous sodium bicarbonate solution (100 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **76d** (480 mg, 1.71 mmol, yield: 69.14%).

MS m/z (ESI): 282.8 [M+1]

Step 5

2-[6-chloro-3-(difluoromethyl)imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **76e**

Compound **76d** (630 mg, 2.24 mmol), Compound **4c** (1.13 g, 3.36 mmol) and cesium carbonate (2.19 g, 6.71 mmol) were dissolved in dioxane (9 mL) and water (3.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (163.77 mg, 223.81 μmol) was added, and the mixture was stirred at 100°C to allow for reacting for 12.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the crude product of title Compound **76e** (1.0 g, 2.44 mmol, yield: 109%).

MS m/z (ESI): 410.0 [M+1]

Step 6

4-[3-(difluoromethyl)-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-*a*]pyridin-6-yl]piperazin-1-tert-butyl carboxylate **76f**

Compound **76e** (200.00 mg, 488.01 μmol), piperazin-1-tert-butyl carboxylate (181.78 mg, 976.01 μmol) and cesium carbonate (477 mg, 1.46 mmol) were dissolved in tert-amyl alcohol (6 mL). Ruphos (45.54 mg, 97.60 μmol) and $Pd_2(dba)_3$ (44.69 mg, 48.80 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **76f** (180 mg, 321.65 μmol, yield: 65.9%).

MS m/z (ESI): 560.2 [M+1]

Step 7

2-[3-(difluoromethyl)-6-(piperazin-1-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **76g**

Compound **76f** (160 mg, 285.9 μmol) was dissolved in methane dioxide (4.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **76g** (160 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 460.2 [M+1]

Step 8

(1*R*,3*S*,4*S*)-3-{4-[3-(difluoromethyl)-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}imidazo[1,5-a]pyridin-6-yl]piperazin-1-carbonyl}-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **76h**

Compound **32a**(88.90 mg, 348.20 μmol) and *N,N*-diisopropylethylamine (135.01 mg, 1.04 mmol, 181.95 μL) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (100.13 mg, 522.30 μmol) and HOBT (70.57 mg, 522.30 μmol). The mixture was stirred at room temperature for 0.5 hours, followed by the addition of the crude product of Compound **76g** (160 mg), and the mixture was further stirred at room temperature for 12 hours. The reaction mixture was diluted with dichloromethane (20 mL), and washed with water (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as

an elution system, to obtain the title Compound **76h** (70 mg, 100.46 μmol, yield: 28.85%).
MS m/z (ESI): 697.3 [M+1]

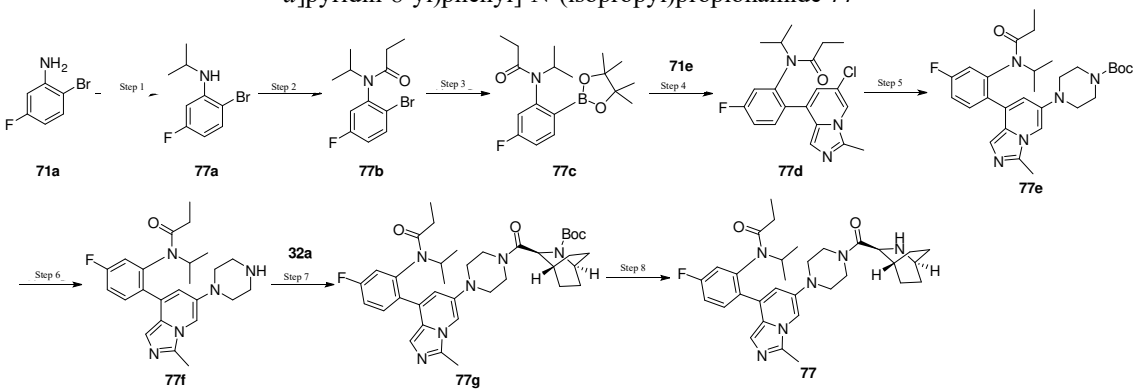
Step 9

N-ethyl-5-fluoro-2-(3-formyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **76**

Compound **76h** (60 mg, 86.11 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 25%-55%), to obtain the title Compound **76** (15 mg, 26.10 μmol, yield: 30.3%) as yellow solid.
MS m/z (ESI): 575.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.97 – 8.88 (m, 1H), 7.74 – 7.67 (m, 1H), 7.59 – 7.38 (m, 3H), 7.31 (s, 1H), 4.04 – 3.94 (m, 1H), 3.87 – 3.53 (m, 5H), 3.17 (br s, 5H), 2.93 – 2.81 (m, 2H), 1.86 – 1.70 (m, 3H), 1.68 – 1.53 (m, 3H), 1.51 – 1.39 (m, 3H), 0.92 (br d, J = 6.3 Hz, 3H), 0.86 – 0.76 (m, 1H), 0.74 – 0.58 (m, 3H), 0.39 – 0.17 (m, 3H).

Example 77

N-[5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)phenyl]-N-(isopropyl)propionamide **77**



Step 1

2-bromo-5-fluoro-*N*-(isopropyl)aniline **77a**

2-Bromo-5-fluoroaniline **71a**(3 g, 15.79 mmol) was dissolved in methanol (40 mL), followed by the addition of acetone (1.83 g, 31.58 mmol) and acetic acid (2.5 g, 41.63 mmol), and the mixture was stirred at 50°C to allow for reacting for 2.0 hours. Sodium cyanoborohydride (2.98 g, 47.37 mmol) was added, and the mixture was stirred at50°C to allow for reacting for 12.0 hours. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (50), concentrated under a reduced pressure to remove the organic solvent, and then extracted with dichloromethane (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **77a** (550 mg, 2.37 mmol, yield: 15.01%) as colorless oil.
MS m/z (ESI): 232.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 2.9, 11.1 Hz, 1H), 7.75 (br s, 1H), 7.48 (dd, J = 5.8, 8.9 Hz, 1H), 6.72 (ddd, J = 3.1, 7.6, 8.8 Hz, 1H), 2.61 (td, J = 7.0, 13.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H).

Step 2

N-(2-bromo-5-fluorophenyl)-*N*-(isopropyl)propionamide **77b**

Compound **77a** (550 mg, 2.37 mmol) was dissolved in toluene (10 mL), followed by the addition of propionyl chloride (438.52 mg, 4.74 mmol) and DMAP(57.90 mg, 473.95 μmol), and the mixture was stirred at 80°C to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **77b** (450 mg, 1.56 mmol, yield: 65.9%) as white solid.
MS m/z (ESI): 289.9 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dd, J = 6.0, 8.9 Hz, 1H), 7.40 (dd, J = 3.0, 9.3 Hz, 1H), 7.30 (dt, J = 3.0, 8.5 Hz, 1H), 4.64 (td, J = 6.8, 13.5 Hz, 1H), 1.81 (dq, J = 1.5, 7.4 Hz, 2H), 1.17 (d, J = 6.6 Hz, 3H), 0.96 – 0.88 (m, 6H).

Step 3

N-[5-fluoro-2-(tetramethyl-1,3,2-dioxaboran-2-yl)phenyl]-*N*-(isopropyl)propionamide **77c**

Compound **77b** (550 mg, 1.91 mmol), potassium acetate (936.62 mg, 9.54 mmol) and bis(pinacolato)diboron (969.38

mg, 3.82 mmol) were dissolved in DMAc (10 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (209.49 mg, 286.30 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 12 hours. After the mixture was cooled to room temperature, 20 mL of water was added, and the mixture was extracted with ethyl acetate (30ml × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **77c** (550 mg, 1.64 mmol, yield: 85.96%) as colorless oil.
MS m/z (ESI): 336.0 [M+1]

Step 4

N-(2-{6-chloro-3-methylimidazo[1,5-a]pyridin-8-yl}-5-fluorophenyl)-*N*-(isopropyl)propionamide **77d**

Compound **71e** (400 mg, 1.63 mmol), Compound **77c**(545 mg, 1.63 mmol) and sodium carbonate (519 mg, 4.90 mmol) were dissolved in dioxane (5 mL) and water (1.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (119 mg, 162.63 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **77d** (150 mg, 401.23 μmol, yield: 24.63%).
MS m/z (ESI): 374.2 [M+1]

Step 5

4-(8-{4-fluoro-2-[*N*-(isopropyl)propionamido]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl}piperazin-1-tert-butyl carboxylate **77e**

Compound **77d** (150 mg, 401.23 μmol), piperazin-1-tert-butyl carboxylate (150 mg, 805.37 μmol) and cesium carbonate (393 mg, 1.21 mmol) were dissolved in tert-amyl alcohol (2 mL). Ruphos (38 mg, 81.43 μmol) and $Pd_2(dba)_3$ (37 mg, 40.41 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **77e** (200 mg, 381.94 μmol, yield: 95.19%) as yellow solid.
MS m/z (ESI): 524.2 [M+1]

Step 6

N-{5-fluoro-2-[3-methyl-6-(piperazin-1-yl)imidazo[1,5-a]pyridin-8-yl]phenyl}-*N*-(isopropyl)propionamide **77f**

Compound **77e** (100 mg, 190.97 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **77f** (120 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 424.4 [M+1]

Step 7

(1*R*,3*S*,4*S*)-3-[4-(8-{4-fluoro-2-[*N*-(isopropyl)propionamido]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **77g**

Compound **32a** (61 mg, 238.93 μmol) and *N,N*-diisopropylethylamine (145 mg, 1.12 mmol) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (65 mg, 339.07 μmol), HOBT (46 mg, 340.43 μmol) and the crude product of Compound **77f** (120 mg), and the mixture was then stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **77g** (50 mg, 75.66 μmol, yield: 33.89%).
MS m/z (ESI): 661.5 [M+1]

Step 8

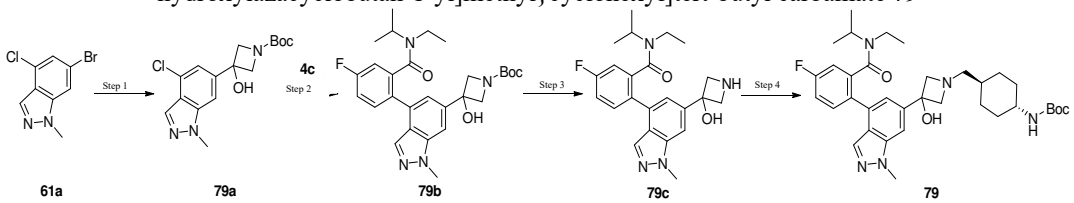
N-[5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)phenyl]-N-(isopropyl)propionamide **77**

Compound **77g** (50 mg, 75.66 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 20%-50%), to obtain the title Compound **77** (7.35 mg, 13.11 μmol, yield: 17.32 %) as yellow solid.
MS m/z (ESI): 561.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 – 7.60 (m, 1H), 7.47 – 7.11 (m, 3H), 6.96 – 6.85 (m, 1H), 6.68 – 6.35 (m, 1H), 4.18 – 3.93 (m, 2H), 3.73 – 3.55 (m, 4H), 3.10 – 2.84 (m, 5H), 2.56 (s, 3H), 2.24 – 2.08 (m, 1H), 2.06 – 1.94

(m, 1H), 1.86 – 1.40 (m, 9H), 1.11 – 0.82 (m, 6H), 0.71 – 0.37 (m, 3H).

Example 79

N-[(1r,4r)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-hydroxylazacyclobutan-1-yl]methyl}cyclohexyl]tert-butyl carbamate **79**



Step 1

3-(4-chloro-1-methyl-1*H*-indazol-6-yl)-3-hydroxylazacyclobutan-1-tert-butyl carboxylate **79a**

6-Bromo-4-chloro-1-methylindazole **61a** (300 mg, 1.22 mmol) was dissolved in THF(6 mL), to which isopropylmagnesium chloride (2M, 1.53 mL) was dropwise added at 0°C, followed by reacting for 2 hours at 50°C. The above mixture was cooled to 22°C, followed by the addition of 3-oxoazacyclobutan-1-tert-butyl carboxylate (732 mg, 4.28 mmol), and the reaction mixture was allowed to react at 22°C for 2 hours. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (50.0 mL × 3), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system. to obtain the crude product of title Compound **79a** (480 mg) as white solid.

MS m/z (ESI): 338.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.74 (s, 1H), 7.29 (s, 1H), 6.59 (s, 1H), 4.17 (d, J = 8.8 Hz, 2H), 4.08 (d, J = 5.2 Hz, 4H), 4.05 (d, J = 4.8 Hz, 1H), 1.42 (s, 9H).

Step 2

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-hydroxylazacyclobutan-1-tert-butyl carboxylate **79b**

Compound **79a** (250 mg, 592 μmol) and Compound **4c**(311 mg, 651μmol) were dissolved in dioxane (20 mL) and water (6 mL). Sodium carbonate (125 mg, 1.18 mmol) and Pd(dppf)Cl_2 (43.3 mg, 59.2 μmol) were added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 7.0 hours. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **79b** (117 mg, 229 μmol, yield: 38.7%) as white solid.

MS m/z (ESI): 510.9 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.73 (s, 1H), 7.61 (dd, J = 8.4, 5.6 Hz, 1H), 7.39 (td, J = 8.8, 2.8 Hz, 1H), 7.31 (ddd, J = 11.6, 9.2, 2.8 Hz, 1H), 7.22 (s, 1H), 6.48 (s, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.11 – 3.99 (m, 6H), 3.42 (dt, J = 13.2, 6.4 Hz, 1H), 3.21 (dd, J = 13.6, 6.8 Hz, 1H), 2.95 – 2.73 (m, 1H), 1.41 (s, 9H), 0.92 (t, J = 25.6 Hz, 3H), 0.68 (dd, J = 11.6, 5.2 Hz, 3.67H), 0.14 (d, J = 6.4 Hz, 2.35H).

Step 3

N-ethyl-5-fluoro-2-[6-(3-hydroxylazacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **79c**

Compound **79b** (75 mg, 146 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **79c** (60 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 411.2 [M+1]

Step 4

N-[(1r,4r)-4-{[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-3-hydroxylazacyclobutan-1-yl]methyl}cyclohexyl]tert-butyl carbamate **79**

The crude product of Compound **79c** (60 mg) and *N*-[(1*r*,4*r*)-4-formylcyclohexyl]tert-butyl carbamate (29.9 mg, 131 μmol) were dissolved in dichloromethane (0.2 mL). The reaction mixture was cooled to 0°C, followed by adding sodium triacetoxyborohydride (83.6 mg, 394 μmol) and stirring at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure, the resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 30%-50%), to obtain the title Compound **79** (35 mg, 56.2 μmol, yield: 42.7 %) as white solid.

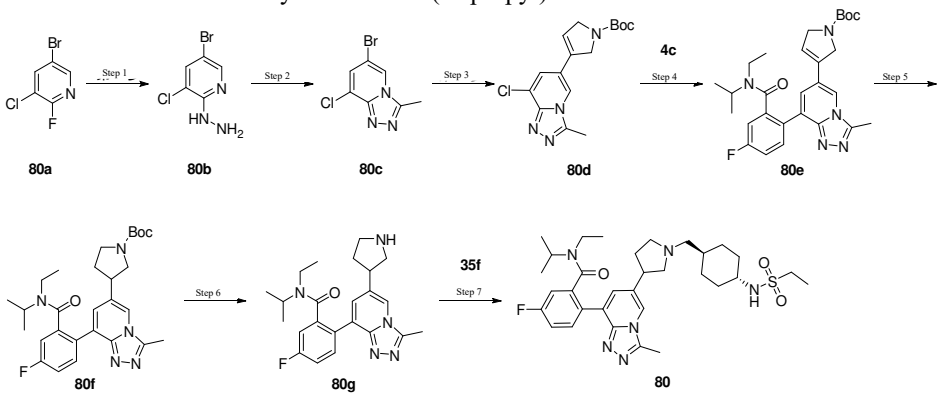
MS m/z (ESI): 622.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 0.51H), 7.80 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.57 (dd, J = 8.4, 5.6 Hz, 1H), 7.45 (d, J = 6.4 Hz, 1H), 7.39 (td, J = 8.8, 2.8 Hz, 1H), 7.29 (ddd, J = 11.6, 9.2, 2.8 Hz, 1H), 6.66

(d, J = 8.0 Hz, 1H), 5.95 (s, 1H), 4.19 (dd, J = 13.6, 6.8 Hz, 0.21H), 4.05 (d, J = 2.4 Hz, 3H), 3.69 (d, J = 7.2 Hz, 1H), 3.54 (d, J = 6.8 Hz, 1H), 3.42 (d, J = 6.4 Hz, 0.85H), 3.26 (d, J = 7.2 Hz, 2H), 3.23 – 3.17 (m, 1H), 3.14 (s, 1H), 2.84 (dt, J = 13.6, 7.2 Hz, 1H), 2.35 (d, J = 6.8 Hz, 2H), 1.87 – 1.66 (m, 4H), 1.36 (s, 9H), 1.25 – 1.06 (m, 3H), 1.05 – 0.89 (m, 2H), 0.89 – 0.58 (m, 7H), 0.12 (d, J = 6.8 Hz, 2H).

Example 80

2-(6-{1-[(4-ethanesulfonamidocyclohexyl)methyl]pyrrolidin-3-yl}-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **80**



Step 1

5-bromo-3-chloro-2-hydrazinopyridine **80b**

5-Bromo-3-chloro-2-fluoropyridine **80a** (2.0 g, 9.5 mmol) was dissolved in ethanol (20 mL), followed by the addition of hydrazine hydrate (4.76 g, 95.04 mmol). The mixture was stirred at 85℃ to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature for solid precipitation, and then filtered, and the filter cake was washed with ethanol (20 mL x 3). The filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **80b** (1.9 g, 8.54 mmol, yield: 89.96%) as white solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 223.9 [M+1]

Step 2

6-bromo-8-chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine **80c**

Compound **80b** (1.4 g, 6.29 mmol) was dissolved in DME(10 mL), followed by the addition of trimethyl orthoformate (6.05 g, 50.34 mmol). The mixture was stirred at 90℃ to allow for reacting for 3.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **80c** (1.3 g, 5.27 mmol, yield: 83.81%) as white solid.

MS m/z (ESI): 247.8 [M+1]

Step 3

3-{8-chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **80d**

Compound **80c** (800 mg, 3.25 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (958 mg, 3.25 mmol) and cesium carbonate (3.17 g, 9.74 mmol) were dissolved in dioxane (9.0 mL) and water (3.0 mL). Pd (dppf)Cl_2 (237.48 mg, 324.55 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **80d** (650 mg, 1.94 mmol, yield: 59.82%).

MS m/z (ESI): 335.0 [M+1]

Step 4

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **80e**

Compound **80d** (640 mg, 1.91 mmol), Compound **4c**(961.21 mg, 2.87 mmol) and cesium carbonate (1.87 g, 5.73 mmol) were dissolved in dioxane (9.0 mL) and water (3.0 mL). Pd(dtbpf)Cl_2 (124.59 mg, 191.16 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl

acetate as an elution system, to obtain the title Compound **80e** (970 mg, 1.91 mmol, yield: 99.97%).
MS m/z (ESI): 508.2 [M+1]

Step 5

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **80f**

Compound **80e** (200 mg, 394.01 μmol) was dissolved in THF (5.0 mL), followed by the addition of Pd/C (47.85 mg, 394.01 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **80f** (160 mg, 313.96 μmol, yield: 79.68%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 510.3 [M+1]

Step 6

N-ethyl-5-fluoro-2-[3-methyl-6-(pyrrolidin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **80g**

Compound **80f** (140 mg, 274.72 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **80g** (110 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 410.2 [M+1]

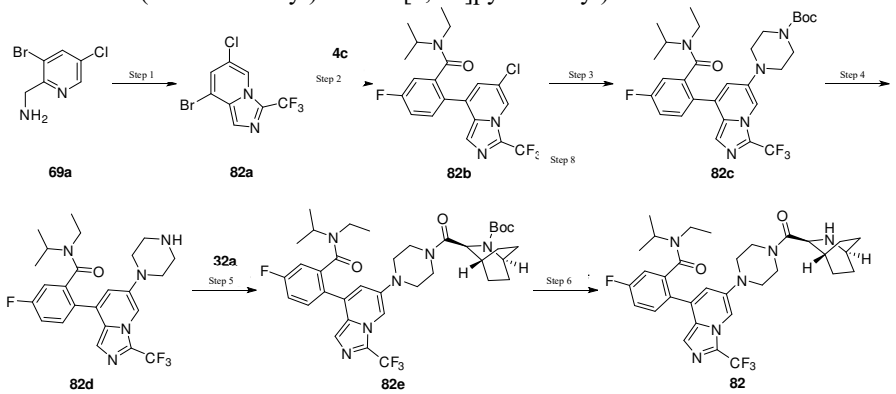
Step 7

2-(6-{1-[(4-ethanesulfonamidocyclohexyl)methyl]pyrrolidin-3-yl}-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **80**

The crude product of Compound **80g** (110 mg), [(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl 4-methylphenyl-1-sulfonate **35f**(201.74 mg, 537.24 μmol), potassium carbonate (185.62 mg, 1.34 mmol) and TBAI(9.92 mg, 26.86 μmol) were dissolved in acetonitrile (2 mL), and the mixture was stirred at 80°C for 12 hours. was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 21%-51%), to obtain the title Compound **80** (80 mg, 130.55 μmol, yield: 48.6%).
MS m/z (ESI): 613.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 1H), 7.35 – 7.19 (m, 2H), 6.99 (d, J = 7.6 Hz, 1H), 3.54 – 3.38 (m, 2H), 3.30 – 3.19 (m, 2H), 3.05 – 2.91 (m, 4H), 2.87 – 2.79 (m, 1H), 2.68 (s, 3H), 2.66 – 2.59 (m, 2H), 2.48 – 2.39 (m, 1H), 2.33 – 2.13 (m, 3H), 1.91 – 1.73 (m, 5H), 1.39 – 1.28 (m, 1H), 1.26 – 1.14 (m, 5H), 0.95 – 0.81 (m, 7H), 0.78 – 0.71 (m, 1H), 0.32 – 0.19 (m, 2H).

Example 82

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}-3-(trifluoromethyl)imidazo[1,5-a]pyridin-8-yl)benzamide **82**



Step 1

8-bromo-6-chloro-3-(trifluoromethyl)imidazo[1,5-a]pyridine **82a**

At 0°C, Compound **69a** (500 mg, 1.94 mmol, hydrochloride) was dissolved in trifluoroacetic anhydride (8.0 mL), followed by the addition of p-toluenesulfonic acid (333.80 mg, 1.94 mmol). The mixture was stirred at 100°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to 0°C, followed by dropwise adding ice water (50 mL) and further stirring for 0.5 hours . The mixture was filtered, the filter cake was dissolved with ethyl acetate (50 mL), and the organic phase was washed with saturated aqueous sodium bicarbonate solution (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting

residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **82a** (300 mg, 1.00 mmol, yield: 51.68%).
MS m/z (ESI): 300.8 [M+1]

Step 2

2-[6-chloro-3-(trifluoromethyl)imidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **82b**

Compound **82a** (300 mg, 1.00 mmol), Compound **4c**(335.81 mg, 1.00 mmol) and sodium carbonate (318.52 mg, 3.01 mmol) were dissolved in dioxane (10 mL) and water (2.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (73.30 mg, 100.18 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, and stirred while slowly adding water (50 mL) to quench the reaction, and the aqueous phase was extracted with ethyl acetate (50 mL * 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **82b** (244 mg, 570.33 μmol, yield: 56.93%).
MS m/z (ESI): 428.1 [M+1]

Step 3

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-(trifluoromethyl)imidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **82c**

Compound **82b** (100 mg, 233.74 μmol), piperazin-1-tert-butyl carboxylate (43.53 mg, 233.74 μmol) and cesium carbonate (228.47 mg, 701.23 μmol) were dissolved in tert-amyl alcohol (5 mL). Ruphos (10.91 mg, 23.37 μmol) and $Pd_2(dba)_3$ (21.40 mg, 23.37 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 120°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and stirred while slowly adding water (20 mL) to quench the reaction, and the aqueous phase was extracted with ethyl acetate (20 mL * 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **82c** (70 mg, 121.19 μmol, yield: 51.85%).
MS m/z (ESI): 578.3 [M+1]

Step 4

N-ethyl-5-fluoro-2-[6-(piperazin-1-yl)-3-(trifluoromethyl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **82d**

Compound **82c** (70 mg, 121.19 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.2 g, 1.75 mmol, 135.14 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 4.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **82d** (57.87 mg, 121.19 μmol, yield: 100%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 478.1 [M+1]

Step 5

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-(trifluoromethyl)imidazo[1,5-a]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **82e**

Compound **32a** (27.11 mg, 106.18 μmol) and *N,N*-diisopropylethylamine (62.38 mg, 482.63 μmol, 84.07 μL) were dissolved in DCM (5.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (27.76 mg, 144.79 μmol) and HOBt (19.56 mg, 144.79 μmol). The mixture was stirred at room temperature for 0.5 hours, followed by the addition of the crude product of Compound **82d** (57.87 mg, 121.19 μmol), and the mixture was further stirred at room temperature for 12 hours. The reaction mixture was quenched by adding water (20 mL), and extracted with ethyl acetate (10 mL x 3). The organic phase was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **82e** (56 mg, 78.34 μmol, yield: 64.6%).
MS m/z (ESI): 715.3 [M+1]

Step 6

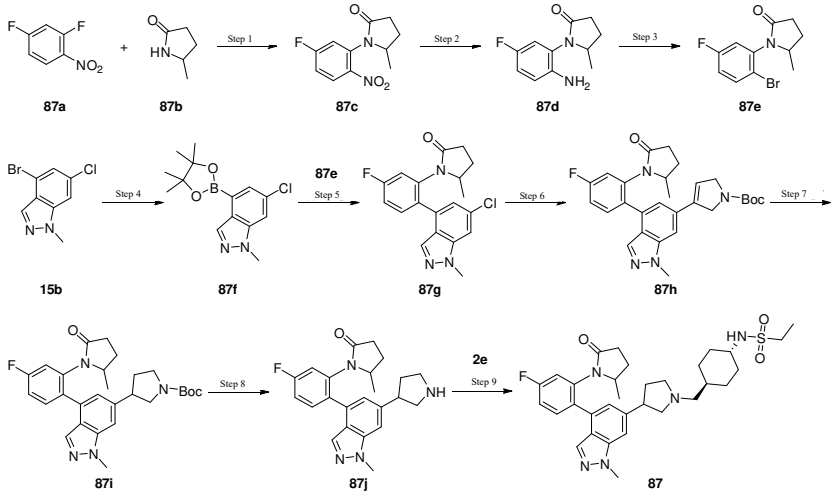
N-ethyl-5-fluoro-*N*-(isopropyl)-2-(6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}-3-(trifluoromethyl)imidazo[1,5-a]pyridin-8-yl)benzamide **82**

Compound **82e** (56 mg, 78.34 μmol) was dissolved in methane dioxide (2.0 mL), and cooled to 0°C, followed by the addition of trifluoroacetic acid (0.2 g, 1.75 mmol, 135.14 μL). The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The residues were dissolved with dichloromethane (10 mL). The organic phase was washed with a 10% aqueous sodium bicarbonate solution (10 mL) and water (10 mL), and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 44%-64%), to

obtain the title Compound **82** (14.57 mg, 23.70 μmol, yield: 30.26 %) as yellow solid.
MS m/z (ESI): 615.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.66 (m, 1H), 7.50 (s, 1H), 7.46 – 7.36 (m, 2H), 7.29 (s, 1H), 7.03 (s, 1H), 3.91 (s, 1H), 3.75 – 3.38 (m, 6H), 3.10 (br s, 5H), 2.89 – 2.78 (m, 2H), 1.80 – 1.39 (m, 9H), 0.96 – 0.62 (m, 7H), 0.36 – 0.29 (m, 2H).

Example 87

N-[(1r,4r)-4-[(3-{4-[4-fluoro-2-(2-methyl-5-oxopyrrolidinyl-1-yl)phenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-yl)methyl]cyclohexyl]ethan-1-sulfonamide **87**



Step 1

1-(5-fluoro-2-nitrophenyl)-5-methylpyrrolidin-2-one **87c**

5-Methylpyrrolidin-2-one **87b** (1.87 g, 18.86 mmol) was dissolved in DMF(30 mL), and cooled to 0°C, followed by the addition of sodium hydride (528.00 mg, 19.80 mmol, 90% purity). The reaction mixture was stirred at room temperature for 1.0 hour and cooled to 0°C, followed by the dropwise addition of the solution of 2,4-difluoro-1-nitrobenzene **87a**(3.0 g, 18.86 mmol) in DMF(30 mL). The mixture was stirred at 0℃ to allow for reacting for 2.0 hours. Water (50 mL) was dropwise added to the reaction mixture, which was then extracted with ethyl acetate (200 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87c** (2.20 g, 9.24 mmol, yield: 48.98%) as yellow solid.
MS m/z (ESI): 239.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (dt, J = 8.8, 6.4 Hz, 1H), 7.55 (dd, J = 10.0, 2.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 4.48 – 4.43 (m, 1H), 2.46 – 2.31 (m, 3H), 1.77 – 1.68 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H).

Step 2

1-(2-amino-5-fluorophenyl)-5-methylpyrrolidin-2-one **87d**

Compound **87c** (2.20 g, 9.24 mmol) was dissolved in methanol (30 mL), followed by the addition of Pd/C (560.82 mg, 4.62 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **87d** (1.67 g, 8.01 mmol, yield: 86.68%) as yellow solid.
MS m/z (ESI): 209.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 8.8, 6.0 Hz, 1H), 7.34 (dd, J = 9.2, 3.2 Hz, 1H), 7.23 (ddd, J = 8.8, 8.4, 3.2 Hz, 1H), 4.16 (dd, J = 13.2, 6.4 Hz, 1H), 2.47 – 2.30 (m, 3H), 1.78 – 1.66 (m, 1H), 1.06 (d, J = 6.4 Hz, 3H).

Step 3

1-(2-bromo-5-fluorophenyl)-5-methylpyrrolidin-2-one **87e**

Compound **87d** (1.51 g, 7.25 mmol) and copper bromide (1.94 g, 8.70 mmol) were dissolved in acetonitrile (70 mL), and cooled to 0°C, followed by the addition of tert-butyl nitrate (1.50 g, 14.50 mmol), and the mixture was stirred at room temperature for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87e** (1.47 g, 5.41 mmol, yield: 74.6%) as yellow oil.
MS m/z (ESI): 272.0 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 8.8, 6.0 Hz, 1H), 7.34 (dd, J = 9.2, 3.2 Hz, 1H), 7.23 (ddd, J = 8.8, 8.4, 3.2 Hz, 1H), 4.16 (dd, J = 13.2, 6.4 Hz, 1H), 2.47 – 2.30 (m, 3H), 1.78 – 1.66 (m, 1H), 1.06 (d, J = 6.4 Hz, 3H).

Step 4

6-chloro-1-methyl-4-(tetramethyl-1,3,2-dioxaboran-2-yl)-1*H*-indazole **87f**

Compound **15b** (1.00 g, 4.07 mmol), potassium acetate (800 mg, 8.15 mmol) and bis(pinacolato)diboron (1.03 g, 4.07 mmol) were dissolved in dioxane (20 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (298 mg, 407 μmol) was added, and the mixture was stirred at 80°C to allow for reacting for 12 hours. The mixture was cooled to room temperature, followed by the addition of water (50 mL) and extraction with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87f** (920 mg, 3.14 mmol, yield: 77.2%) as white solid.

MS m/z (ESI): 393.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 0.8 Hz, 1H), 8.00 (dd, J = 1.6, 1.0 Hz, 1H), 7.38 (d, J = 1.6 Hz, 1H), 4.04 (d, J = 6.0 Hz, 3H), 1.35 (s, 12H).

Step 5

1-[2-(6-chloro-1-methyl-1*H*-indazol-4-yl)-5-fluorophenyl]-5-methylpyrrolidin-2-one **87g**

Compound **87f** (500 mg, 1.71 mmol) and Compound **87e** (465 mg, 1.71 mmol) were dissolved in dioxane (28 mL) and water (4.0 mL). Sodium carbonate (362 mg, 3.42 mmol) and Pd(dppf)Cl_2 (125 mg, 170 μmol) were added, and the mixture was stirred at 80 °C under a nitrogen atmosphere to allow for reacting for 6.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87g** (460 mg, 1.29 mmol, yield: 75.2%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.73 (s, 1H), 7.57 (s, 1H), 7.37 (s, 1H), 7.29 (dd, J = 9.6, 2.8 Hz, 1H), 7.03 (d, J = 1.2 Hz, 1H), 4.07 (s, 3H), 3.08 (s, 1H), 2.32 (ddd, J = 16.8, 9.2, 4.4 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.79 (s, 1H), 1.46 – 1.35 (m, 1H), 0.77 (d, J = 6.4 Hz, 3H).

Step 6

3-{4-[4-fluoro-2-(2-methyl-5-oxopyrrolidinyl-1-yl)phenyl]-1-methyl-1*H*-indazol-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **87h**

Compound **87g** (340 mg, 950 μmol) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (308 mg, 1.05 mmol) were dissolved in dioxane (4.0 mL) and water (0.8 mL). Sodium carbonate (201 mg, 1.90 mmol) and Pd (dppf)Cl_2 (69.5 mg, 95.02 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87h** (300 mg, 611 μmol, yield: 64.3%) as yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.65 (m, 2H), 7.62 – 7.54 (m, 1H), 7.36 (td, J = 8.4, 2.8 Hz, 1H), 7.30 – 7.22 (m, 2H), 6.44 (d, J = 9.2 Hz, 1H), 4.53 (s, 2H), 4.25 (s, 2H), 4.10 (d, J = 2.0 Hz, 3H), 3.04 (s, 1H), 2.31 (ddd, J = 16.4, 8.8, 4.4 Hz, 1H), 2.05 (dd, J = 17.2, 8.4 Hz, 1H), 1.74 (s, 1H), 1.47 (d, J = 9.2 Hz, 9H), 1.37 (dd, J = 18.4, 13.6 Hz, 1H), 0.78 – 0.70 (m, 3H).

Step 7

3-{4-[4-fluoro-2-(2-methyl-5-oxopyrrolidinyl-1-yl)phenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-tert-butyl formate **87i**

Compound **87h** (250 mg, 509 μmol) was dissolved in ethanol (10 mL), followed by the addition of Pd/C (80.0 mg, 752 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **87i** (186 mg, 377 μmol, yield: 74.1%) as yellow solid.

MS m/z (ESI): 493.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 4.8 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.35 (td, J = 8.4, 2.4 Hz, 1H), 7.26 (dd, J = 10.0, 2.4 Hz, 1H), 6.95 (s, 1H), 4.06 (s, 3H), 3.77 (dd, J = 10.0, 8.0 Hz, 1H), 3.52 (d, J = 8.0 Hz, 2H), 3.33 (s, 1H), 3.28 – 3.15 (m, 1H), 3.03 (s, 1H), 2.29 (dd, J = 16.8, 7.6 Hz, 2H), 2.18 – 2.00 (m, 2H), 1.78 (s, 1H), 1.41 (d, J = 3.6 Hz, 10H), 0.71 (dd, J = 6.0, 3.2 Hz, 3H).

Step 8

1-{5-fluoro-2-[1-methyl-6-(pyrrolidin-3-yl)-1*H*-indazol-4-yl]phenyl}-5-methylpyrrolidin-2-one **87j**

Compound **87i** (80.0 mg, 162.41 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **87j** (60 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 393.2 [M+1]

Step 9

N-[(1r,4r)-4-[(3-{4-[4-fluoro-2-(2-methyl-5-oxopyrrolidinyl-1-yl)phenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-yl)methyl]cyclohexyl]ethan-1-sulfonamide **87**

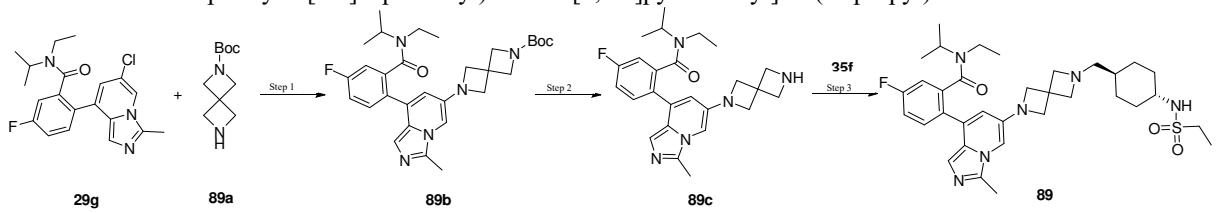
The crude product of Compound **87j** (60 mg), potassium iodide (25.4 mg, 153 μmol) and potassium carbonate (42.3 mg, 306 μmol) were dissolved in DMAc (3.0 mL), followed by the addition of Compound **2e** (79.4 mg, 168 μmol), and the mixture was stirred at 80°C to allow for reacting for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 30%-40%), to obtain the title Compound **87** (3.40 mg, 5.71 μmol, yield: 22.7%) as white solid.

MS m/z (ESI): 596.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.53 (ddd, J = 8.6, 6.4, 4.4 Hz, 2H), 7.33 (td, J = 8.4, 2.8 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.99 (dd, J = 12.0, 5.2 Hz, 2H), 4.03 (s, 3H), 3.46 (s, 2H), 3.02 – 2.88 (m, 5H), 2.67 (s, 2H), 2.44 (d, J = 8.8 Hz, 1H), 2.27 (d, J = 7.2 Hz, 4H), 2.12 – 2.02 (m, 1H), 1.83 (d, J = 13.2 Hz, 6H), 1.36 (dd, J = 18.8, 10.4 Hz, 2H), 1.18 (td, J = 7.2, 4.4 Hz, 4H), 0.89 (m, 2H), 0.72 (dd, J = 6.0, 3.2 Hz, 3H).

Example 89

N-ethyl-5-fluoro-2-[3-methyl-6-(6-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-2,6-diazaspirocyclo[3.3]heptan-2-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **89**



29g **89a** **89b** **89c** **89**

Step 1

6-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-2,6-diazaspirocyclo[3.3]heptan-2-tert-butyl carboxylate **89b**

Compound **29g** (200 mg, 534.97 μmol), 2,6-diazaspirocyclo[3.3]heptan-2-tert-butyl carboxylate (106.06 mg, 534.97 μmol) and cesium carbonate (889 mg, 2.73 mmol) were dissolved in tert-amyl alcohol (3.0 mL). Ruphos (49.93 mg, 106.99 μmol) and Pd_2 $(dba)_3$ (48.99 mg, 53.50 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 110°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the reverse phase preparative column chromatography (column: C8; mobile phase: acetonitrile, water, elution gradient: 45%-55%), to obtain the title Compound **89b** (350 mg, 653.41 μmol, yield: 71.85%).

MS m/z (ESI): 536.5[M+1]

Step 2

2-(6-{2,6-diazaspirocyclo[3.3]heptan-2-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **89c**

Compound **89b** (250 mg, 466.72 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **89c** (200 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 436.3 [M+1]

Step 3

N-ethyl-5-fluoro-2-[3-methyl-6-(6-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-2,6-diazaspirocyclo[3.3]heptan-2-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **89**

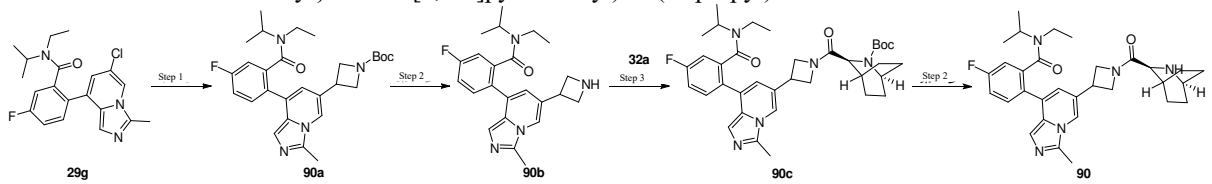
Compound **89c** (100 mg, 181.96 μmol, trifluoroacetate) was dissolved in acetonitrile (2.0 mL), followed by the addition of [(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl4-methylphenyl-1-sulfonate **35f** (136 mg, 362.18 μmol), potassium carbonate (126 mg, 911.66 μmol) and TBAI(7 mg, 18.95 μmol), and the mixture was stirred at 80°C for 12 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:27%-57%), to obtain the title Compound **89** (4.76 mg, 7.45 μmol, yield: 4.09%) as yellow solid.

MS m/z (ESI): 639.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.61 (m, 1H), 7.40 – 7.27 (m, 2H), 6.99 – 6.94 (m, 2H), 6.26 – 6.19 (m, 1H), 3.82 (s, 4H), 3.47 – 3.38 (m, 2H), 3.21 (s, 4H), 3.01 – 2.89 (m, 4H), 2.52 – 2.51 (m, 3H), 2.19 – 2.12 (m, 2H), 1.89 – 1.79 (m, 2H), 1.75 – 1.66 (m, 2H), 1.20 – 1.11 (m, 6H), 0.94 – 0.72 (m, 9H), 0.31 – 0.26 (m, 2H).

Example 90

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **90**



Step 1

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **90a**

Compound **29g** (500 mg, 1.34 mmol), potassium (1-(tert-butoxycarbonyl)azacyclobutan-3-yl)trifluoroborate (351.89 mg, 1.34 mmol) and cesium carbonate (1.31 g, 4.01 mmol) were dissolved in water (0.5 mL) and toluene (5.0 mL). Ruphos (70 mg, 150.01 μmol) and Pd_2 (dba)$_3$ (122.47 mg, 133.74 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **90a** (150 mg, 303.28 μmol, yield: 22.68%) as yellow solid.

MS m/z (ESI): 495.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (br dd, J = 5.6, 8.4 Hz, 1H), 7.42 – 7.30 (m, 3H), 7.10 – 7.02 (m, 1H), 6.73 – 6.65 (m, 1H), 4.20 (br d, J = 6.6 Hz, 2H), 3.97 – 3.84 (m, 2H), 3.83 – 3.73 (m, 1H), 3.54 – 3.42 (m, 1H), 2.97 (br s, 2H), 2.60 (s, 3H), 1.40 (s, 9H), 0.90 – 0.72 (m, 7H), 0.33 (br d, J = 6.4 Hz, 2H).

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **90b**

Compound **90a** (150 mg, 303.28 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **90b** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 395.3 [M+1]

Step 3

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **90c**

(1*R*,3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.2]octan-3-carboxylic acid **32a**(51 mg, 199.76 μmol) and *N,N*-diisopropylethylamine (80 mg, 618.99 μmol) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (57 mg, 297.34 μmol), HOBT (40 mg, 296.03 μmol) and Compound **90b** (100 mg), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **90c** (120 mg, 189.94 μmol, yield: 62.6%).

MS m/z (ESI): 632.4 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **90**

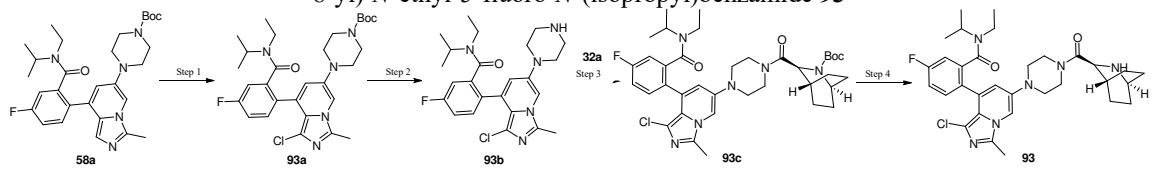
Compound **90c** (120 mg, 189.94 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 8-9 with ammonia water, and then purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 14%-44%), to obtain the title Compound **90** (31.39 mg, 59.04 μmol, yield: 31.08%) as yellow solid.

MS m/z (ESI): 532.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 7.99 (m, 1H), 7.74 – 7.63 (m, 1H), 7.43 – 7.27 (m, 2H), 7.12 – 7.01 (m, 1H), 6.78 – 6.61 (m, 1H), 4.69 – 3.78 (m, 6H), 3.65 – 3.57 (m, 1H), 3.50 – 3.41 (m, 1H), 3.02 – 2.86 (m, 1H), 2.80 – 2.73 (m, 1H), 2.60 (s, 3H), 1.83 – 1.34 (m, 9H), 1.12 – 0.67 (m, 7H), 0.34 – 0.25 (m, 2H).

Example 93

2-(1-chloro-3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **93**



Step 1

4-(1-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **93a**

Compound **58a** (400 mg, 763.88 μmol) and NCS (122.40 mg, 916.66 μmol) were dissolved in acetonitrile (3.0 mL). The mixture was stirred at 80°C to allow for reacting for 12 hours. Ethyl acetate (50 mL) was added to the reaction mixture, which was then washed with water (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **93a** (200 mg, 358.37 μmol, yield: 46.91%).

MS m/z (ESI): 558.3 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.11 – 6.98 (m, 2H), 6.84 – 6.79 (m, 1H), 6.70 – 6.65 (m, 1H), 3.71 – 3.62 (m, 1H), 3.56 – 3.46 (m, 4H), 3.45 – 3.36 (m, 1H), 3.09 – 2.98 (m, 2H), 2.90 – 2.81 (m, 2H), 2.70 – 2.69 (m, 2H), 2.54 – 2.48 (m, 3H), 1.41 (s, 9H), 0.97 – 0.73 (m, 7H), 0.39 – 0.32 (m, 2H).

Step 2

2-[1-chloro-3-methyl-6-(piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **93b**

Compound **93a** (60 mg, 107.51 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **93b** (60 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 458.1 [M+1]

Step 3

(1*R*,3*S*,4*S*)-3-[4-(1-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **93c**

(1*R*,3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.2]octan-3-carboxylic acid **32a**(26.78 mg, 104.90 μmol) and *N,N*-diisopropylethylamine (40.67 mg, 314.69 μmol, 54.81 μL) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (30.16 mg, 157.34 μmol), HOBT (21.26 mg, 157.34 μmol) and the crude product of Compound **93b** (60 mg), and the mixture was then stirred at room temperature for 12 hours. Dichloromethane (20 mL) was added to the reaction mixture, and the organic phases were washed with water (20 mL x 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **93c** (40 mg, 57.53 μmol, yield: 54.85 %).

MS m/z (ESI): 695.3 [M+1]

Step 4

2-(1-chloro-3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **93**

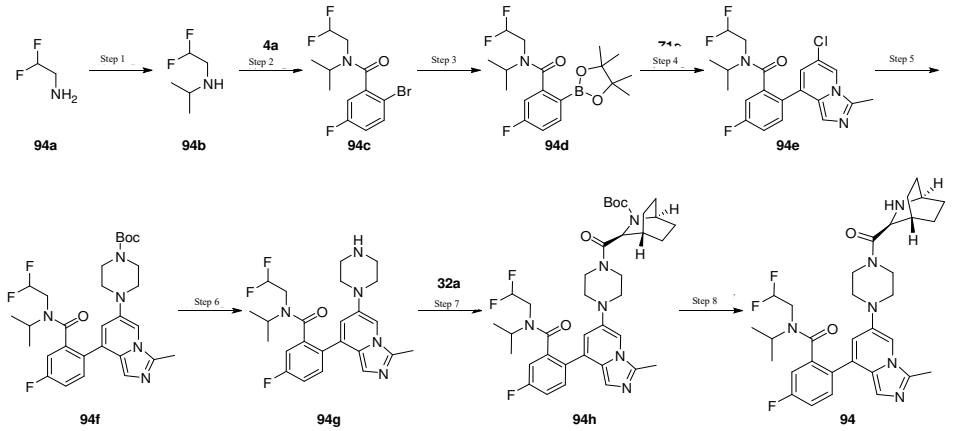
Compound **93c** (60 mg, 86.30 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **93** (30 mg, 50.41 μmol, yield: 58.41 %) as yellow solid.

MS m/z (ESI): 595.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.39 (m, 1H), 7.38 – 7.28 (m, 3H), 6.61 (br s, 1H), 3.99 – 3.90 (m, 1H), 3.81 – 3.43 (m, 6H), 3.15 – 2.90 (m, 5H), 2.85 (br s, 1H), 2.55 (s, 3H), 1.87 – 1.70 (m, 3H), 1.68 – 1.55 (m, 3H), 1.51 – 1.38 (m, 3H), 1.07 – 0.73 (m, 7H), 0.35 – 0.25 (m, 2H).

Example 94

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **94**



Step 1

(2,2-difluoroethyl)(isopropyl)amine **94b**

2,2-difluoroethyl-1-amine **94a** (10 g, 123.36 mmol, 8.70 mL) was dissolved in acetone (15 mL), followed by the addition of 10% Pd/C (2.19 g, 20.60 mmol). Under a hydrogen atmosphere (45 PSI), the mixture was heated to 50°C and stirred to allow for reacting for 12.0 hours . The reaction mixture was filtered through diatomite, and washed with methanol. The filtrate was concentrated to 50 mL, and the resulting mixture was regulated to PH = 2 with 2M hydrochloric acid . The mixture was concentrated under a reduced pressure, to obtain the hydrochloride of title Compound **94b** (12.0 g, 97.45 mmol, yield: 78.99%) as white solid.

MS m/z (ESI): 124.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 – 9.62 (m, 1H), 6.69 – 6.36 (m, 1H), 3.54 – 3.43 (m, 2H), 3.40 – 3.30 (m, 1H), 1.32 – 1.21 (m, 6H).

Step 2

2-bromo-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **94c**

Compound **4a** (9 g, 41.09 mmol), Compound **94b** (9.84 g, 61.64 mmol, hydrochloride) and DIPEA(15.93 g, 123.28 mmol, 21.47 mL) were dissolved in dichloromethane (120 mL). The mixture was cooled to 0°C, followed by the addition of HATU (23.44 g, 61.64 mmol). The mixture was stirred at 25°C for 12 hours. A saturated aqueous sodium carbonate solution (120 mL) was added to the reaction mixture, which was then extracted with dichloromethane (80ml×3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **94c** (5 g, 15.43 mmol, yield37.54%) as white solid.

MS m/z (ESI): 323.7 [M+1]

Step 3

N-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **94d**

Compound **94c** (2 g, 6.17 mmol), potassium acetate (1.82 g, 18.51 mmol) and bis(pinacolato)diboron (4.70 g, 18.51 mmol) were dissolved in DMSO(40 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (451.48 mg, 617.02 μmol) was added, and the mixture was stirred at 100°C to allow for reacting for 12 hours. After the mixture was cooled to room temperature, 80 mL of water was added, and the mixture was extracted with ethyl acetate (80ml × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain residues, i.e., crude products, which were then purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **94d** (2.5 g, 6.73 mmol, yield: 109%).

MS m/z (ESI): 372.2 [M+1]

Step 4

2-{6-chloro-3-methylimidazo[1,5-a]pyridin-8-yl}-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **94e**

Compound **71e** (450 mg, 1.83 mmol), Compound **94d**(1.13 g, 1.83 mmol) and sodium carbonate (582.82 mg, 5.50 mmol) were dissolved in dioxane (12 mL) and water (2.0 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (134.12 mg, 183.30 μmol) was added, and the mixture was stirred at 95°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **94e** (410 mg, 1.00 mmol, yield: 54.58%).

MS m/z (ESI): 410.2 [M+1]

Step 5

4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl}piperazin-1-tert-butyl carboxylate **94f**

Compound **94e** (410 mg, 1.00 mmol), piperazin-1-tert-butyl carboxylate (372.65 mg, 2.00 mmol) and cesium carbonate (977.86 mg, 3.00 mmol) were dissolved in tert-amyl alcohol (7.0 mL). Ruphos (93.36 mg, 200.08 μmol) and Pd_2 (dba)$_3$ (91.61 mg, 100.04 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **94f** (460 mg, 821.98 μmol, yield: 82.16%) as yellow oil.

MS m/z (ESI): 560.3 [M+1]

Step 6

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(piperazin-1-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **94g**

Compound **94f** (150 mg, 268.04 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **94g** (155 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 460.1 [M+1]

Step 7

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **94h**

Compound **32a** (75.27 mg, 294.80 μmol) and *N,N*-diisopropylethylamine (242.46 mg, 1.88 mmol) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (77.58 mg, 404.68 μmol), HOBT (55.41 mg, 410.04 μmol) and the crude product of Compound **94g** (155 mg), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium carbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **94h** (130 mg, 186.57 μmol, yield: 69.61%).

MS m/z (ESI): 697.4 [M+1]

Step 8

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{4-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]piperazin-1-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **94**

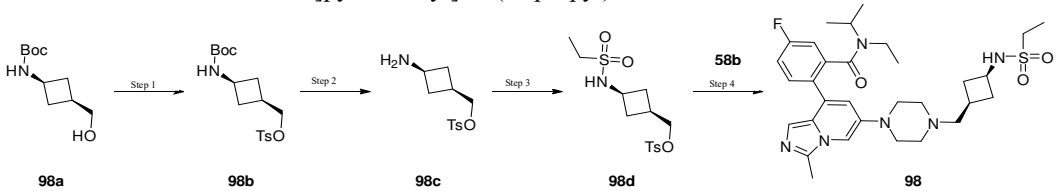
Compound **94h** (130 mg, 186.57 μmol) was dissolved in methane dioxide (2.0 mL) and trifluoroacetic acid (0.75 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compound **94** (32.3 mg, 54.13 μmol, yield: 29.01 %) as yellow solid.

MS m/z (ESI): 597.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 – 7.61 (m, 1H), 7.49 – 7.25 (m, 3H), 6.95 (s, 1H), 6.65 – 6.52 (m, 1H), 5.95 – 5.52 (m, 1H), 3.94 (s, 1H), 3.82 – 3.43 (m, 7H), 3.15 – 2.74 (m, 6H), 2.71 – 2.53 (m, 3H), 1.90 – 1.21 (m, 10H), 1.03 – 0.84 (m, 3H), 0.33 (s, 2H).

Example 98

N-ethyl-5-fluoro-2-[3-methyl-6-(4-{[(1*s*,3*s*)-3-ethanesulfonamidocyclobutyl]methyl}piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **98**



Step 1

N-[(1*s*,3*s*) -3-{[(4-methylphenylsulfonyl)oxy]methyl}cyclobutyl]tert-butyl carbamate **98b**

N-[(1*s*,3*s*)-3-(hydroxymethyl)cyclobutyl]tert-butyl carbamate **98a** (200 mg, 993.73 μmol), triethylamine (301.67 mg, 2.98 mmol, 415.52 μL) and DMAP(12.14 mg, 99.37 μmol) were dissolved in dichloromethane (4 mL), and cooled to 0°C, followed by the addition of 4-toluensulfonyl chloride (227.34 mg, 1.19 mmol), and the mixture was stirred at room temperature for 12 hours. Dichloromethane (40 mL) was added to the reaction mixture, which was then

washed with water (40 mL×3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **98b** (300 mg, 844.01 μmol, yield: 84.93%) as white solid.
MS m/z (ESI): 378.0 [M+23]

Step 2

[(1*s*,3*s*)-3-aminocyclobutyl]methyl-4-methylbenzen-1-sulfonate **98c**

Compound **98b** (300 mg, 844.01 μmol) was dissolved in dichloromethane (3.0 mL), and cooled to 0°C, followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **98c** (300 mg) as colorless oil.
MS m/z (ESI): 256.0 [M+1]

Step 3

[(1*s*,3*s*)-3-ethanesulfonamidocyclobutyl]methyl4-methylbenzen-1-sulfonate **98d**

The crude product of Compound **98c** (300 mg) was dissolved in dichloromethane (5 mL), followed by the dropwise addition of triethylamine (246.57 mg, 2.44 mmol, 339.62 μL), and then the slow dropwise addition of ethanesulfonyl chloride (125.32 mg, 974.67 μmol, 92.35 μL). The mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with dichloromethane (40 mL), and washed with water (40 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **98d** (200 mg, 575.62 μmol, yield: 70.87%) as white solid.
MS m/z (ESI): 347.9 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (br d, J = 9.1 Hz, 1H), 4.02 – 3.96 (m, 2H), 3.89 – 3.76 (m, 1H), 3.04 – 2.95 (m, 2H), 2.53 – 2.49 (m, 1H), 2.49 – 2.48 (m, 3H), 2.48 – 2.44 (m, 1H), 2.35 – 2.22 (m, 1H), 1.83 – 1.70 (m, 2H), 1.40 – 1.32 (m, 3H).

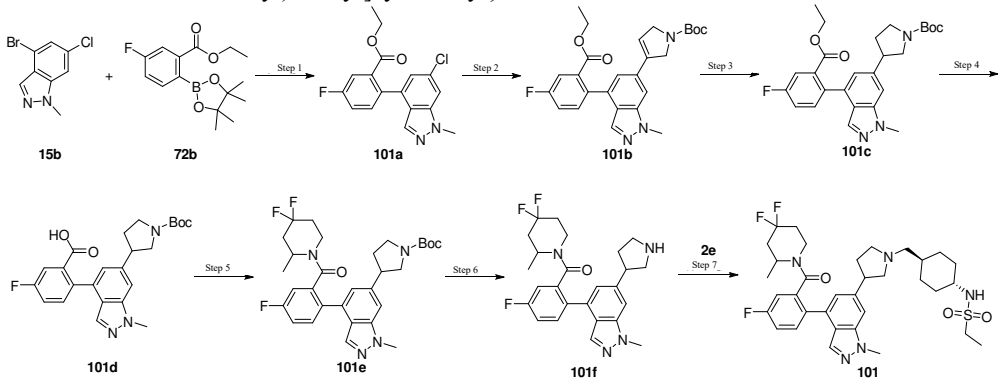
Step 4

N-ethyl-5-fluoro-2-[3-methyl-6-(4-{[(1*s*,3*s*)-3-ethanesulfonamidocyclobutyl]methyl}piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **98**

Compound **58b** (90 mg, 167.43 μmol, trifluoroacetate) was dissolved in acetonitrile (2.0 mL), followed by the addition of Compound **98d** (116.34 mg, 334.85 μmol), potassium carbonate (115.70 mg, 837.13 μmol) and TBAI(6.18 mg, 16.74 μmol), and the mixture was stirred at 80°C for 12 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:24%-54%), to obtain the title Compound **98** (40 mg, 66.80 μmol, yield: 39.9 %) as yellow solid.
MS m/z (ESI): 599.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.63 (m, 1H), 7.40 – 7.22 (m, 4H), 6.99 – 6.93 (m, 1H), 6.63 – 6.56 (m, 1H), 3.64 – 3.52 (m, 1H), 3.48 – 3.39 (m, 1H), 3.08 – 2.82 (m, 7H), 2.57 – 2.51 (m, 3H), 2.46 (br s, 4H), 2.42 – 2.25 (m, 5H), 2.13 – 2.01 (m, 1H), 1.66 – 1.53 (m, 2H), 1.17 (t, J = 7.3 Hz, 3H), 1.12 – 0.99 (m, 1H), 0.90 (br d, J = 6.6 Hz, 3H), 0.81 (t, J = 6.9 Hz, 2H), 0.76 – 0.68 (m, 1H), 0.34 – 0.25 (m, 2H).

Example 101

N-{4-[(3-{4-[2-(4,4-difluoro-2-methylpiperidin-1-carbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-yl)methyl]cyclohexyl}ethan-1-sulfonamide **101**



Step 1

2-(6-chloro-1-methyl-1*H*-indazol-4-yl)-5-ethyl fluorobenzoate **101a**

Compound 1**5b** (1.00 g, 4.07 mmol) and Compound **72b** (1.32 g, 4.48 mmol) were dissolved in dioxane (18 mL) and water (2.0 mL). Sodium carbonate (1.30 g, 12.22 mmol) and Pd(dppf)Cl_2 (298 mg, 407 μmol) were added, and the mixture was stirred at 70 °C under a nitrogen atmosphere to allow for reacting for 16 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **101a** (1.21 g, 3.64 mmol, yield: 81.2%) as faint yellow solid.

MS m/z (ESI): 333.0 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.72 – 7.65 (m, 2H), 7.63 – 7.53 (m, 2H), 7.01 (d, J = 1.6 Hz, 1H), 4.06 (s, 3H), 3.92 (q, J = 7.2 Hz, 2H), 0.80 (t, J = 7.2 Hz, 3H).

Step 2

3-{4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **101b**

Compound **101a** (1.10 g, 3.31 mmol) and 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (1.46 g, 4.96 mmol) were dissolved in dioxane (18 mL) and water (2 mL). Sodium carbonate (1.05 g, 9.92 mmol) and Pd (dppf)Cl_2 (242 mg, 331 μmol) were added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **101b** (916 mg, 1.97 mmol, yield: 59.5%) as white solid.

MS m/z (ESI): 466.2 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.51 (m, 5H), 7.23 (d, J = 11.6 Hz, 1H), 6.51 (d, J = 12.4 Hz, 1H), 4.54 (s, 2H), 4.25 (s, 2H), 4.10 (d, J = 2.0 Hz, 3H), 3.89 (dd, J = 14.8, 7.6 Hz, 2H), 1.47 (d, J = 9.6 Hz, 9H), 0.76 (t, J = 7.6 Hz, 3H).

Step 3

3-{4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-tert-butyl formate **101c**

Compound **101b** (910 mg, 1.95 mmol) was dissolved in ethanol (40 mL), followed by the addition of Pd/C (303 mg). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 4.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **101c** (909 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 468.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.47 (m, 5H), 6.92 (s, 1H), 4.34 (s, 0.29H), 4.10 – 4.00 (m, 3H), 3.94 – 3.84 (m, 2H), 3.76 (dd, J = 10.0, 8.0 Hz, 1H), 3.52 (t, J = 9.2 Hz, 2H), 3.44 (dd, J = 6.8, 4.4 Hz, 1H), 3.30 – 3.24 (m, 0.70H), 2.26 (d, J = 5.2 Hz, 1H), 2.09 (dd, J = 20.4, 10.4 Hz, 1H), 1.41 (d, J = 6.4 Hz, 9H), 0.76 (dd, J = 15.6, 7.2 Hz, 3H).

Step 4

2-(6-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluorobenzoic acid **101d**

Compound **101c** (900 mg, 1.93 mmol) was dissolved in methanol (14 mL) and water (6.0 mL), followed by the addition of LiOH.H_2O (230 mg, 9.63 mmol), and the mixture was stirred at 30°C to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting mixture was purified by the reverse phase preparative column chromatography (C18 column; mobile phase: acetonitrile, water, elution gradient: 40%-55%), to obtain the title Compound **101d** (822 mg, 1.87 mmol, yield: 97.1%) as white solid.

MS m/z (ESI): 440.1[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.56 (m, 5H), 6.97 (s, 1H), 4.05 (s, 3H), 3.81 – 3.73 (m, 1H), 3.52 (t, J = 9.2 Hz, 2H), 3.34 (s, 1H), 3.27 (s, 1H), 2.26 (s, 1H), 2.14 – 2.01 (m, 1H), 1.41 (d, J = 5.6 Hz, 9H).

Step 5

3-{4-[2-(4,4-difluoro-2-methylpiperidin-1-carbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-tert-butyl formate **101e**

Compound **101d** (200 mg, 455 μmol) was dissolved in DMF (4.0 mL), followed by the addition of DIPEA (235 mg, 1.82 mmol) and 4,4-difluoro-2-dimethylpiperidine(67.7 mg, 501 μmol, hydrochloride). The mixture was cooled to 0°C, followed by the addition of HATU (208 mg, 546 μmol). The reaction mixture was stirred at room temperature for 1.0 hour, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **101e** (160 mg, 287 μmol, yield: 63.1%) as white solid.

MS m/z (ESI): 557.2 [M+1]

Step 6

4-[2-(4,4-difluoro-2-methylpiperidin-1-carbonyl)-4-fluorophenyl]-1-methyl-6-(pyrrolidin-3-yl)-1*H*-indazole **101f**

Compound **101e** (160 mg, 287 μmol) was dissolved in methane dioxide (2.4 mL), followed by the addition of trifluoroacetic acid (0.8 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **101f** (130 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 457.2 [M+1]

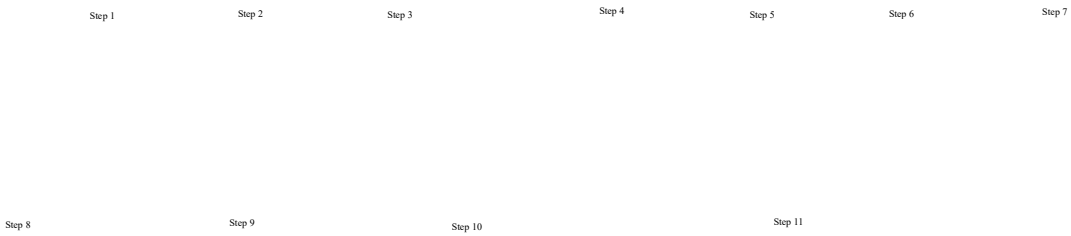
Step 7

N-{4-[(3-{4-[2-(4,4-difluoro-2-methylpiperidin-1-carbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}pyrrolidin-1-yl)methyl]cyclohexyl}ethan-1-sulfonamide **101**

The crude product of Compound **101f** (130 mg) was dissolved in *N,N*-dimethylformamide (2.0 mL), followed by the addition of potassium carbonate (118 mg, 854 μmol), potassium iodide (47.3 mg, 285 μmol) and Compound **2e** (148 mg, 313 μmol), and the mixture was stirred at 80°C to allow for reacting for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% trifluoroacetic acid), elution gradient: 10%-40%), to obtain the title Compound **101** (68.3 mg, 104 μmol, yield: 36.3%) as white solid.
MS m/z (ESI): 660.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.62 (s, 2H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.10 (s, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 4.50 (m, 1H), 4.07 (s, 4H), 3.76 (m, 3H), 3.43 – 3.35 (m, 1H), 3.32 – 3.02 (m, 5H), 2.98 (q, *J* = 7.2 Hz, 2H), 2.48 – 2.43 (m, 1H), 2.29 – 1.61 (m, 9H), 1.39 – 0.96 (m, 9H), 0.45 (s, 2H).

Example 107

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **107**



Step 1

5-{1-[(tert-butoxy)carbonyl]azacyclobutan-3-yl}-3-chloropyridin-2-methyl carboxylate **107c**

5-Bromo-3-chloropyridin-2-methyl carboxylate **107a** (10 g, 39.92 mmol), 3-bromoazacyclobutan-1-tert-butyl carboxylate **107b** (12.25 g, 51.90 mmol), Ir[dF(CF_3)ppy]$_2$(dtbpy) (PF_6) (448 mg, 399.24 μmol), $NiCl_2$.dtbbpy (238 mg, 598.86 μmol), tris(trimethylsilyl)silane (9.95 g, 40.00 mmol) and sodium carbonate (8.46 g, 79.85 mmol) were dissolved in dimethoxyethane (480 mL), and the reaction mixture was placed under a 10W LED bluelight lamp, and stirred to allow for reacting for 3.0 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were dissolved in ethyl acetate (100 mL), and washed with water (400 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107c** (8.7 g, 26.62 mmol, yield: 66.69%) as yellow oil.
MS m/z (ESI): 327.0 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 1.8 Hz, 1H), 7.82 (br d, *J* = 1.5 Hz, 1H), 4.40 (t, *J* = 8.8 Hz, 2H), 4.01 (s, 3H), 3.95 (dd, *J* = 5.6, 8.6 Hz, 2H), 3.83 – 3.74 (m, 1H), 1.50 – 1.44 (m, 9H).

Step 2

3-[5-chloro-6-(hydroxylmethyl)pyridin-3-yl]azacyclobutan-1-tert-butyl carboxylate **107d**

Compound **107c** (7.7 g, 23.56 mmol) was dissolved in methanol (77 mL) and tetrahydrofuran (77 mL), and cooled to 0°C, followed by the addition of sodium borohydride (2.77 g, 73.28 mmol). The mixture was stirred at room temperature to allow for reacting for 3.0 hour. The reaction mixture was cooled to 0°C, a saturated aqueous ammonium chloride solution (500 mL) was added to quench the reaction, methanol and tetrahydrofuran were removed under a reduced pressure, and the aqueous phase was extracted with ethyl acetate (500 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude

product of title Compound **107d** (6 g, 20.08 mmol, yield: 85.23%) as yellow oil. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 299.0 [M+1]

Step 3

3-{5-chloro-6-[(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)methyl]pyridin-3-yl}azacyclobutan-1-tert-butyl carboxylate **107e**

Compound **107d** (5.5 g, 18.41 mmol), 2,3-dihydro-1*H*-isoindol-1,3-dione (2.99 g, 20.34 mmol) and triphenylphosphine (7.25 g, 27.63 mmol) were dissolved in tetrahydrofuran (70 mL), and cooled to 0°C under a nitrogen atmosphere, followed by the addition of DIAD (5.58 g, 27.58 mmol). The mixture was stirred at room temperature to allow for reacting for 12 hour. The reaction mixture was diluted with ethyl acetate (500 mL), and washed with water (500 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107e** (7 g, 16.36 mmol, yield: 88.87%) as colorless oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 – 8.29 (m, 1H), 8.04 (d, J = 1.8 Hz, 1H), 7.97 – 7.87 (m, 4H), 5.02 – 4.96 (m, 2H), 4.24 – 4.15 (m, 2H), 3.94 – 3.79 (m, 3H), 1.45 – 1.34 (m, 9H).

Step 4

3-[6-(aminomethyl)-5-chloropyridin-3-yl]azacyclobutan-1-tert-butyl carboxylate **107f**

Compound **107e** (7 g, 16.36 mmol) was dissolved in the solution of methylamine in ethanol (29.93 g, 289.09 mmol, 33.29 mL, 30%). The mixture was stirred at 65°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure, to obtain the crude product of title Compound **107f** (4.87 g, 16.35 mmol, yield: 100%) as light yellow oil. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 298.0 [M+1]

Step 5

3-[5-chloro-6-(acetamidomethyl)pyridin-3-yl]azacyclobutan-1-tert-butyl carboxylate **107g**

Compound **107f** (4.87 g, 16.35 mmol) was dissolved in dichloromethane (70 mL), followed by the addition of triethylamine (4.96 g, 49.06 mmol). The reaction mixture was cooled to 0°C, followed by dropwise adding acetyl chloride (1.54 g, 19.63 mmol) slowly and stirring at room temperature to allow for reacting for 1.0 hour. The reaction mixture was diluted with dichloromethane (300 mL), and washed with water (300 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **107g** (6 g, 17.66 mmol, yield: 107.96%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 340.0 [M+1]

Step 6

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **107h**

Compound **107g** (3 g, 8.83 mmol) was dissolved in dichloromethane (40 mL), followed by the addition of a Burgess reagent (2.31 g, 9.71 mmol). The mixture was stirred at 40°C to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding dichloromethane (100 mL) and washing with water (100 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **107h** (2 g, 6.22 mmol, yield: 70.4%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 3.1 Hz, 2H), 6.88 – 6.82 (m, 1H), 4.35 (t, J = 8.8 Hz, 2H), 4.03 – 3.91 (m, 2H), 3.73 – 3.60 (m, 1H), 2.67 (s, 3H), 1.50 (s, 9H).

Step 7

3-{8-chloro-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **107i**

Compound **107h** (200 mg, 621.50 μmol) was dissolved in tetrahydrofuran (3.0 mL), followed by the addition of pyridine (73.74 mg, 932.25 μmol, 75.40 μL). The mixture was cooled to -40°C, a Selectfluor fluridizer (279.62 mg, 789.31 μmol) was added, and the mixture was stirred at -40°C to allow for reacting for 0.5 hours. A saturated aqueous sodium thiosulfate solution (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **107i** (60 mg, 176.58 μmol, yield: 28.4%).
MS m/z (ESI): 340.1 [M+1]

Step 8

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-6-

yl)azacyclobutan-1-tert-butyl formate **107j**

Compound **107i** (120 mg, 353.16 μmol), Compound **4c**(295.96 mg, 529.74 μmol) and potassium phosphate (224.89 mg, 1.06 mmol) were dissolved in dioxane (2.0 mL) and water (0.4 mL). $Pd(dtbpf)Cl_2$ (23.02 mg, 35.32 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107j** (120 mg, 234.11 μmol, yield: 66.3%).

MS m/z (ESI): 513.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.53 (dt, J = 2.7, 5.6 Hz, 1H), 7.40 – 7.27 (m, 2H), 6.53 (s, 1H), 4.18 (br s, 2H), 3.74 (br s, 3H), 3.55 – 3.42 (m, 1H), 3.32 (br dd, J = 6.5, 13.1 Hz, 1H), 3.03 – 2.88 (m, 1H), 2.54 (s, 3H), 1.39 (s, 9H), 1.00 – 0.74 (m, 7H), 0.43 (br s, 2H).

Step 9

2-[6-(azacyclobutan-3-yl)-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **107k**

Compound **107j** (120 mg, 234.11 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **107k** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 413.2 [M+1]

Step 10

(1*R*,3*S*,4*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **107l**

(1*R*,3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.2]octan-3-carboxylic acid **32a**(61 mg, 238.93 μmol) and *N,N*-diisopropylethylamine (95 mg, 735.07 μmol) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (58 mg, 302.56 μmol), HOBT (42 mg, 310.83 μmol) and Compound **107k** (123 mg, 233.62 μmol, trifluoroacetate), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107l** (70 mg, 107.73 μmol, yield: 46.11%).

MS m/z (ESI): 650.4 [M+1]

Step 11

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **107**

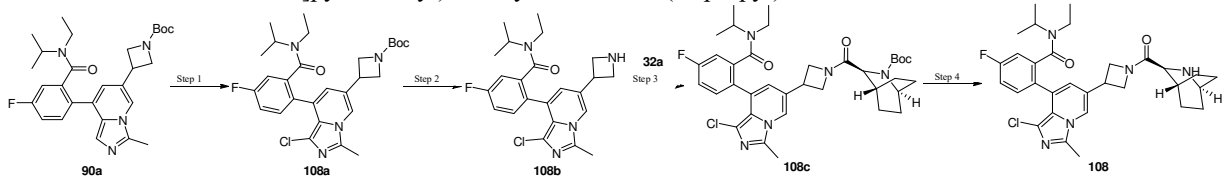
Compound **107l** (70 mg, 107.73 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 8-9 with ammonia water, and then purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 24%-54%), to obtain the title Compound **107** (29.9 mg, 54.40 μmol, yield: 50.49%) as yellow solid.

MS m/z (ESI): 550.3[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 88.03 – 7.86 (m, 1H), 7.58 – 7.25 (m, 3H), 6.64 – 6.42 (m, 1H), 4.67 – 3.77 (m, 6H), 3.66 – 3.53 (m, 1H), 3.51 – 3.41 (m, 1H), 3.02 – 2.72 (m, 2H), 2.55 (s, 3H), 1.83 – 1.33 (m, 9H), 1.08 – 0.63 (m, 7H), 0.50 – 0.31 (m, 2H).

Example 108

2-(1-chloro-3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **108**



Step 1

3-(1-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **108a**

Compound **90a** (680 mg, 1.37 mmol), acetic acid (180 mg, 3.00 mmol, 171.59 μL) and NCS (238.66 mg, 1.79 mmol)

were dissolved in trichloromethane (10 mL). The mixture was stirred at room temperature to allow for reacting for 12 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **108a** (450 mg, 850.59 μmol, yield: 61.87%).

MS m/z (ESI): 529.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (br s, 1H), 7.51 – 7.40 (m, 1H), 7.39 – 7.27 (m, 2H), 6.69 (s, 1H), 4.20 (br d, J = 5.0 Hz, 2H), 3.99 – 3.74 (m, 3H), 3.65 – 3.50 (m, 1H), 3.41 – 3.33 (m, 1H), 2.87 (br dd, J = 6.6, 13.2 Hz, 1H), 2.60 (s, 3H), 1.40 (s, 10H), 1.06 – 0.70 (m, 7H), 0.27 (br d, J = 6.3 Hz, 2H).

Step 2

2-[6-(azacyclobutan-3-yl)-1-chloro-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **108b**

Compound **108a** (110 mg, 207.92 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **108b** (110 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 429.2 [M+1]

Step 3

(1*R*,3*S*,4*S*)-3-[3-(1-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **108c**

(1*R*,3*S*,4*S*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.2]octan-3-carboxylic acid **32a**(53.94 mg, 211.28 μmol) and *N,N*-diisopropylethylamine (84.61 mg, 654.70 μmol, 114.03 μL) were dissolved in DCM (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (60.29 mg, 314.49 μmol), HOBT (42.31 mg, 313.11 μmol) and the crude product of Compound **108b** (110 mg), and the mixture was then stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **108c** (92.1 mg, 138.24 μmol, yield: 66.5 %).

MS m/z (ESI): 666.4 [M+1]

Step 4

2-(1-chloro-3-methyl-6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **108**

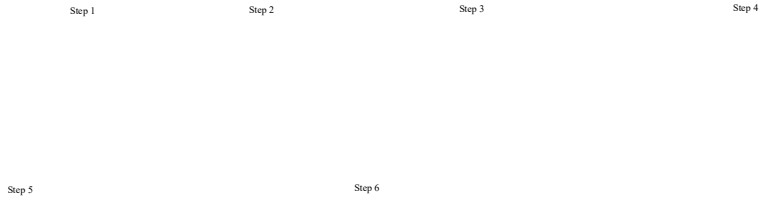
Compound **108c** (92.1 mg, 138.24 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 37%-67%), to obtain the title Compound **108** (35.11 mg, 62.02 μmol, yield: 44.86 %) as yellow solid.

MS m/z (ESI): 566.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 – 8.03 (m, 1H), 7.50 – 7.26 (m, 3H), 6.76 – 6.58 (m, 1H), 4.67 – 3.79 (m, 6H), 3.65 – 3.51 (m, 2H), 2.94 – 2.71 (m, 2H), 2.59 (s, 3H), 1.82 – 1.37 (m, 9H), 1.06 – 0.66 (m, 7H), 0.32 – 0.20 (m, 2H).

Example 110

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}pyrrolo[1,2-*a*]pyrazin-8-yl)benzamide **110**



Step 1

6,8-dibromopyrrolo[1,2-a]pyrazine **110b**

Pyrrolo[1,2-a]pyrazine **110a** (2 g, 16.93 mmol) was dissolved in DCM (80 mL), followed by the addition of NBS (6.06 g, 34.03 mmol). The mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (70 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **110b** (4.58 g, 16.60 mmol, yield: 98.04%) was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 276.9[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.12 (dd, J = 1.1, 4.9 Hz, 1H), 7.72 (d, J = 5.0 Hz, 1H), 7.31 (s, 1H).

Step 2

4-{8-bromopyrrolo[1,2-a]pyrazin-6-yl}-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **110c**

Compound **110b** (1 g, 3.62 mmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (1.01 g, 3.26 mmol) and sodium carbonate (1.15 g, 10.87 mmol) were dissolved in dioxane (10 mL) and water (2 mL). Pd (dppf)Cl_2 (265.18 mg, 362.41 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **110c** (497 mg, 1.31 mmol, yield: 36.25%).

MS m/z (ESI): 380.2 [M+1]

Step 3

4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **110d**

Compound **110c** (497 mg, 1.31 mmol) and Compound **4c**(1 g, 1.49 mmol) were dissolved in dioxane (8 mL) and water (2.0 mL). Sodium carbonate (417.78 mg, 3.94 mmol) and Pd(dppf)Cl_2 (96.14 mg, 131.39 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **110d** (540 mg, 1.07 mmol, yield: 81.13%).

MS m/z (ESI): 507.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.36 (br d, J = 4.4 Hz, 1H), 7.25 (m, 4H), 6.95 – 6.85 (m, 1H), 6.23 – 6.04 (m, 1H), 4.30 – 3.96 (m, 3H), 3.57 (br d, J = 5.6 Hz, 2H), 3.41 – 3.34 (m, 1H), 3.29 (br s, 2H), 2.97 – 2.74 (m, 1H), 1.44 (s, 9H), 1.08 – 0.66 (m, 7H), 0.23 (br d, J = 6.4 Hz, 2H).

Step 4

N-ethyl-5-fluoro-*N*-(isopropyl)-2-[6-(1,2,3,6-tetrahydropyridin-4-yl)pyrrolo[1,2-a]pyrazin-8-yl]benzamide **110e**

Compound **110d** (200 mg, 335.56 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **110e** (150 mg, 369.01 μmol, yield: 110%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 407.1 [M+1]

Step 5

(1*R*,3*S*,4*S*)-3-[4-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)-1,2,3,6-tetrahydropyridin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **110f**

Compound **32a** (67.00 mg, 262.42 μmol) and *N,N*-diisopropylethylamine (161.39 mg, 1.25 mmol, 217.51 μL) were dissolved in dichloromethane (3 mL), and cooled to 0°C. EDCI (71.82 mg, 374.63 μmol), HOBT (50.62 mg, 374.63 μmol) and Compound **110e** (130 mg, 249.75 μmol, trifluoroacetic acid) were added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **110f** (100 mg, 155.33 μmol, yield: 62.19%).

MS m/z (ESI): 644.4 [M+1]

Step 6

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(6-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}pyrrolo[1,2-a]pyrazin-8-yl)benzamide **110**

Compound **110f** (100 mg, 155.33 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction

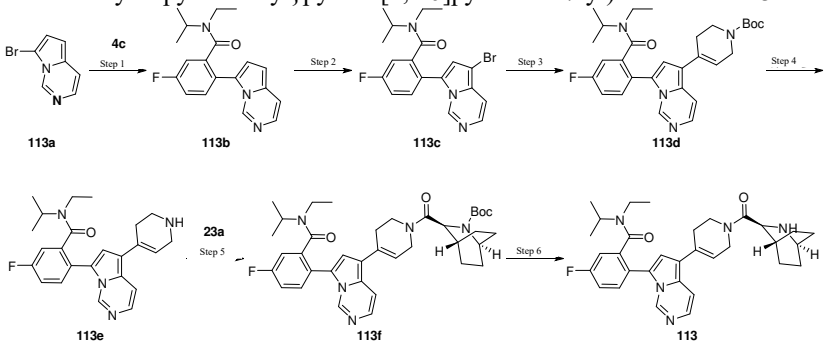
mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 22%-52%), and the obtained isomer mixture was purified by the preparative SFC (separation column: DAICEL CHIRALPAK IA (250 mm * 30 mm,10 um); mobile phase: 25-25% (v/v) Heptane-EtOH:CAN=4:1 (0.1%IPA)), to obtain the title Compound **110** (29.69 mg, 54.61 μmol, yield: 37.11%).

MS m/z (ESI): 544.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.37 (br s, 1H), 7.61 (m, 1H), 7.57 – 7.51 (m, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.23 (m, 1H), 6.94 – 6.89 (m, 1H), 6.26 – 6.11 (m, 1H), 4.39 – 4.07 (m, 2H), 4.02 – 3.86 (m, 1H), 3.73 – 3.58 (m, 1H), 3.40 – 3.31 (m, 2H), 2.95 – 2.71 (m, 2H), 2.58 – 2.52 (m, 1H), 2.46 (m, 1H), 1.89 – 1.23 (m, 10H), 1.09 – 0.68 (m, 7H), 0.23 (m, 2H).

Example 113

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(5-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}pyrrolo[1,2-*c*]pyrimidin-7-yl)benzamide **113**



Step 1

N-ethyl-5-fluoro-*N*-(isopropyl)-2-{pyrrolo[1,2-*c*]pyrimidin-7-yl}benzamide **113b**

7-Bromopyrrolo[1,2-*c*]pyrimidine **113a** (500 mg, 2.54 mmol) and Compound **4c** (2.55 g, 3.81 mmol) were dissolved in dioxane (3 mL) and water (1.0 mL). Cesium carbonate (2.48 g, 7.61 mmol) and Pd(dppf)Cl_2 (165.39 mg, 253.77 μmol) were added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **113b** (900 mg, 2.77 mmol, yield: 109%).

MS m/z (ESI): 326.0 [M+1]

Step 2

2-{5-bromopyrrolo[1,2-c]pyrimidin-7-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **113c**

Compound **113b** (800 mg, 2.46 mmol) was dissolved in DCM (24 mL), followed by the addition of NBS(437.60 mg, 2.46 mmol). The mixture was stirred at room temperature for 12 hours. Dichloromethane (100 mL) was added to the reaction mixture, which was then washed with water (100 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **113c** (620 mg, 1.53 mmol, yield: 62.4%).

MS m/z (ESI): 404.0[M+1]

Step 3

4-(7-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-c]pyrimidin-8-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **113d**

Compound **113c** (300 mg, 742.07 μmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (344.18 mg, 1.11 mmol) and cesium carbonate (725.34 mg, 2.23 mmol) were dissolved in dioxane (3 mL) and water (1 mL). Pd (dppf)Cl_2 (54.30 mg, 74.21 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **113d** (290 mg, 572.43 μmol, yield: 77.14%).

MS m/z (ESI): 507.2 [M+1]

Step 4

N-ethyl-5-fluoro-*N*-(isopropyl)-2-[5-(1,2,3,6-tetrahydropyridin-4-yl)pyrrolo[1,2-c]pyrimidin-7-yl]benzamide **113e**

Compound **113d** (290 mg, 572.43 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for

reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **113e** (290 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 407.1 [M+1]

Step 5

(1*R*,3*S*,4*S*)-3-[4-(7-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-c]pyrimidin-5-yl)-1,2,3,6-tetrahydropyridin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **113f**

Compound **32a** (142.24 mg, 557.14 μmol) and *N,N*-diisopropylethylamine (216.02 mg, 1.67 mmol, 291.13 μL) were dissolved in dichloromethane (3 mL), and cooled to 0°C. EDCI (160.21 mg, 835.71 μmol) and HOBT (112.92 mg, 835.71 μmol) were added, and the mixture was stirred at room temperature for 0.5 hours. The crude product of Compound **113e** (290 mg) was added, and the mixture was stirred at room temperature for 12 hours. Dichloromethane (50 mL) was added to the reaction mixture, which was then washed with water (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **113f** (150 mg, 233.00 μmol, yield: 41.82 %).
MS m/z (ESI): 644.3 [M+1]

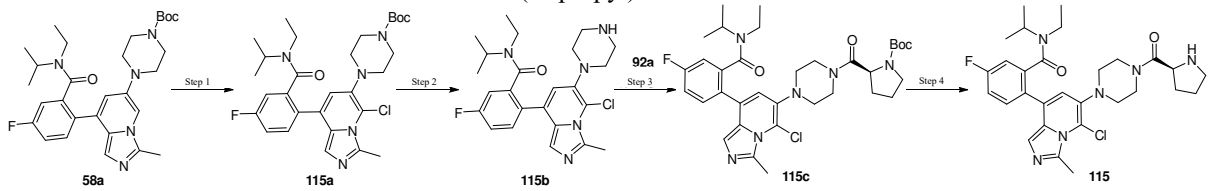
Step 6

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(5-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}pyrrolo[1,2-*c*]pyrimidin-7-yl)benzamide **113**

Compound **113f** (150 mg, 233.00 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 42%-72%), to obtain the title Compound **113** (50 mg, 91.97 μmol, yield: 39.47%).
MS m/z (ESI): 544.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 – 8.67 (m, 1H), 7.76 – 7.65 (m, 1H), 7.61 (br d, J = 6.4 Hz, 1H), 7.45 – 7.31 (m, 3H), 6.94 – 6.85 (m, 1H), 6.06 – 5.91 (m, 1H), 4.29 – 4.01 (m, 2H), 3.97 – 3.83 (m, 1H), 3.72 – 3.51 (m, 2H), 3.43 (td, J = 6.5, 13.1 Hz, 1H), 3.31 (br dd, J = 6.6, 13.1 Hz, 2H), 2.89 – 2.74 (m, 2H), 2.55 (br s, 1H), 1.87 – 1.23 (m, 10H), 1.00 – 0.57 (m, 7H), 0.32 (br d, J = 4.5 Hz, 2H).

Example 115

2-(5-chloro-3-methyl-6-{4-[(2*S*)-pyrrolidin-2-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **115**



Step 1

4-(5-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-tert-butyl carboxylate **115a**

Compound **58a** (1 g, 1.72 mmol) and NCS(222.62 mg, 1.67 mmol) was dissolved in dichloromethane (10 mL). Under a nitrogen atmosphere, the mixture was stirred at 20°Cto allow for reacting for 1.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **115a** (710 mg, 1.27 mmol, yield: 74.02%).
MS m/z (ESI): 558.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 – 7.59 (m, 1H), 7.43 – 7.30 (m, 2H), 7.09 (s, 1H), 6.73 – 6.62 (m, 1H), 3.54 – 3.38 (m, 5H), 3.30 – 3.21 (m, 1H), 2.99 – 2.94 (m, 3H), 2.88 – 2.79 (m, 4H), 2.58 – 2.54 (m, 1H), 1.46 – 1.37 (m, 9H), 1.20 – 1.04 (m, 1H), 0.98 – 0.88 (m, 3H), 0.84 – 0.74 (m, 3H), 0.39 – 0.32 (m, 2H).

Step 2

2-[5-chloro-3-methyl-6-(piperazin-1-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **115b**

Compound **115a** (150 mg, 268.78 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **115b** (123 mg). The crude product was directly used in the next step of reaction without

purification.
MS m/z (ESI): 458.3 [M+1]

Step 3

(2*S*)-2-[4-(5-chloro-8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-carbonyl]-pyrrolidin-1-tert-butyl carboxylate **115c**

(2*S*)-1-[(tert-butoxy)carbonyl]pyrrolidin-2-carboxylic acid **92a** (50.95 mg, 236.72 μmol) and *N,N*-diisopropylethylamine (194.69 mg, 1.51 mmol) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (62.29 mg, 324.95 μmol), HOBT (44.49 mg, 329.26 μmol) and the crude product of Compound **115b** (123 mg), and the mixture was then stirred at room temperature for 12 hours. A saturated aqueous sodium carbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **115c** (120 mg, 183.15 μmol, yield: 68.2%).
MS m/z (ESI): 655.2 [M+1]

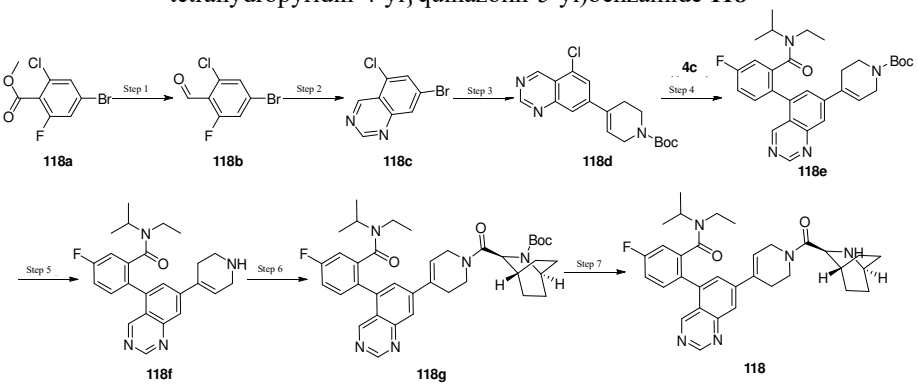
Step 4

2-(5-chloro-3-methyl-6-{4-[(2*S*)-pyrrolidin-2-carbonyl]piperazin-1-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **115**

Compound **115c** (120 mg, 183.15 μmol) was dissolved in methane dioxide (2.0 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 29%-59%), to obtain the title Compound **115** (3.06 mg, 5.51 μmol, yield: 3.01%) as green solid.
MS m/z (ESI): 555.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 – 7.61 (m, 1H), 7.42 – 7.31 (m, 2H), 7.08 (s, 1H), 6.71 – 6.67 (m, 1H), 3.90 – 3.83 (m, 1H), 3.63 (s, 4H), 3.48 – 3.39 (m, 2H), 2.97 (s, 4H), 2.93 – 2.82 (m, 5H), 2.68 – 2.60 (m, 1H), 2.04 – 1.94 (m, 1H), 1.70 – 1.53 (m, 3H), 1.23 (s, 1H), 0.95 – 0.89 (m, 3H), 0.85 – 0.74 (m, 4H), 0.38 – 0.33 (m, 2H).

Example 118

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(7-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}quinazolin-5-yl)benzamide **118**



Step 1

4-bromo-2-chloro-6-fluorobenzaldehyde **118b**

Methyl 4-bromo-2-chloro-6-fluorobenzoate **118a**(2 g, 7.48 mmol) was dissolved in dichloromethane (56.36 mL), cooled to -78°C, followed by the slow dropwise addition of DIBAL-H (3.19 g, 22.43 mmol). The reaction mixture was stirred at -65°C to allow for reacting for 2.0 hours . Methanol (5.0 mL) was dropwise added to the reaction mixture, which was further stirred for 0.5 hours. Methanol (2 mL), a 10% aqueous sodium hydroxide solution (2 mL) and water (2 mL) were added to the reaction mixture, which was then warmed to room temperature, followed by the addition of anhydrous sodium sulfate (20 g) and further stirring for 0.5 hours. The mixture was filtered, and the filtrate was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the title Compound **118b** (1.67 g, 7.03 mmol, yield: 94.1%; purity: 66%).
MS m/z (ESI): 238.9 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.72 (s, 2H).

Step 2

7-bromo-5-chloroquinazoline **118c**

Compound **118b** (200 mg, 842.27 μmol) and formamidine acetate (263.07 mg, 2.53 mmol) were dissolved in

acetonitrile (10 mL). Potassium carbonate (582.05 mg, 4.21 mmol) was added, and the mixture was stirred at 110°C at for 12 hours. The reaction mixture was cooled to room temperature, quenched by adding water (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **118c** (102 mg, 418.91 μmol, yield: 49.7%).
MS m/z (ESI): 243.0[M+1]

Step 3

4-(5-chloroquinazolin-7-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **118d**

Compound **118c** (102 mg, 418.91 μmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (129.53 mg, 418.91 μmol) and sodium carbonate (133.20 mg, 1.26 mmol) were dissolved in dioxane (5 mL) and water (1 mL). Pd (dppf)Cl_2 (30.65 mg, 41.89 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, quenched by adding water (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **118d** (61 mg, 176.39 μmol, yield: 42.1%).
MS m/z (ESI): 346.1 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 9.34 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 6.37 (br s, 1H), 4.17 (br d, J = 2.1 Hz, 2H), 3.69 (t, J = 5.6 Hz, 2H), 2.63 (br s, 2H), 1.50 (s, 9H).

Step 4

4-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}quinazolin-7-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **118e**

Compound **118d** (61 mg, 176.39 μmol) and Compound **4c** (73.91 mg, 176.39 μmol) were dissolved in dioxane (5 mL) and water (1.0 mL). Sodium carbonate (56.09 mg, 529.17 μmol) and Pd(dppf)Cl_2 (12.91 mg, 17.64 μmol) were added, and the mixture was stirred at 100 °C under a nitrogen atmosphere to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, quenched by adding water (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **118e** (51 mg, 98.34 μmol, yield: 55.75%).
MS m/z (ESI): 519.3 [M+1]

Step 5

N-ethyl-5-fluoro-*N*-(isopropyl)-2-[7-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-5-yl]benzamide **118f**

Compound **118e** (150 mg, 289.23 μmol) was dissolved in dichloromethane (5 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (10 mL), and extracted with dichloromethane (10 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **118f** (120 mg, 286.73 μmol, yield: 99.14%) was obtained. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 419.3 [M+1]

Step 6

(1*R*,3*S*,4*S*)-3-[4-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}quinazolin-7-yl)-1,2,3,6-tetrahydropyridin-1-carbonyl]-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **118g**

Compound **32a** (57.53 mg, 225.34 μmol) and *N,N*-diisopropylethylamine (145.61 mg, 1.13 mmol) were dissolved in dichloromethane (5.1 mL), and cooled to 0°C. EDCI (64.80 mg, 338.01 μmol) and HOBT (64.80 mg, 338.01 μmol) were added, and the mixture was stirred at room temperature for 1.0 hours. The crude product of Compound **118f** (120 mg, 286.73 μmol) was added, and the mixture was stirred at room temperature for 12 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **118g** (102 mg, 155.54 μmol, yield: 54.2%).
MS m/z (ESI): 656.4 [M+1]

Step 7

N-ethyl-5-fluoro-*N*-(isopropyl)-2-(7-{1-[(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.2]octan-3-carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}quinazolin-5-yl)benzamide **118**

Compound **118g** (102 mg, 155.54 μmol) was dissolved in methane dioxide (5.0 mL) and trifluoroacetic acid (1.48 g,

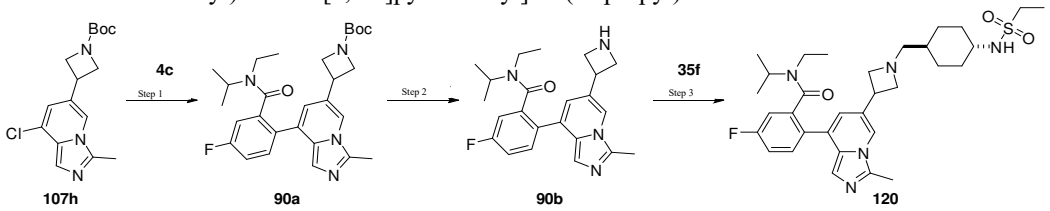
12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of a saturated aqueous sodium carbonate solution (10 mL), and the reaction mixture was extracted with ethyl acetate (5 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **118** (14.34 mg, 25.81 μmol, yield: 16.59%).

MS m/z (ESI): 556.2 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 9.42 – 9.09 (m, 2H), 8.10 – 7.80 (m, 2H), 7.69 – 7.54 (m, 1H), 7.46 – 7.24 (m, 2H), 6.66 – 6.50 (m, 1H), 4.59 – 4.42 (m, 2H), 4.40 – 4.28 (m, 1H), 4.26 – 4.04 (m, 1H), 3.83 – 3.77 (m, 1H), 3.49 (s, 1H), 2.85 – 2.74 (m, 2H), 2.24 – 2.13 (m, 1H), 2.08 – 1.98 (m, 3H), 1.91 – 1.83 (m, 2H), 1.75 – 1.69 (m, 1H), 1.67 – 1.55 (m, 2H), 1.29 (s, 3H), 1.04 – 0.86 (m, 5H), 0.73 – 0.63 (m, 2H), 0.31 – 0.23 (m, 1H), 0.13 - -0.03 (m, 2H).

Example 120

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **120**



Step 1

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **90a**

Compound **107h** (400 mg, 1.24 mmol), Compound **4c**(909.12 mg, 1.49 mmol) and potassium phosphate (791.54 mg, 3.73 mmol) were dissolved in dioxane (8.0 mL) and water (2.0 mL). Pd(dtbpf)Cl_2 (81.01 mg, 124.30 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **90a** (584 mg, 1.18 mmol, yield: 94.99%).

MS m/z (ESI): 495.2[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (br s, 1H), 7.77 – 7.59 (m, 1H), 7.46 – 7.25 (m, 2H), 7.05 (s, 1H), 6.67 (br s, 1H), 4.20 (br d, J = 5.4 Hz, 2H), 3.98 – 3.72 (m, 3H), 3.48 (br s, 1H), 3.29 (br d, J = 7.1 Hz, 1H), 3.07 – 2.86 (m, 1H), 2.59 (s, 3H), 1.40 (s, 9H), 1.21 – 1.11 (m, 1H), 0.97 – 0.70 (m, 6H), 0.32 (br d, J = 6.1 Hz, 2H).

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **90b**

Compound **90a** (150 mg, 303.28 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **90b** (154 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 395.2 [M+1]

Step 3

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **120**

Compound **90b** (154 mg, 302.85 μmol, trifluoroacetate) was dissolved in DMSO(2.0 mL), followed by the addition of [(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl4-methylphenyl-1-sulfonate **35f** (227.55 mg, 605.69 μmol), potassium carbonate (300 mg, 2.17 mmol) and TBAI(11.19 mg, 30.28 μmol), and the mixture was stirred at 100°C for 4.0 hours. The reaction mixture was filtered, concentrated under a reduced pressure, and the resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient:5%-35%), to obtain the title Compound **120** (7.6 mg, 12.71 μmol, yield: 4.20%) as yellow solid.

MS m/z (ESI): 598.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.00 – 7.90 (m, 1H), 7.73 – 7.61 (m, 1H), 7.43 – 7.27 (m, 2H), 7.07 – 6.94 (m, 2H), 6.84 – 6.74 (m, 1H), 3.73 – 3.54 (m, 3H), 3.51 – 3.38 (m, 1H), 3.36 – 3.12 (m, 3H), 3.03 – 2.84 (m, 4H), 2.59 (s, 3H), 2.40 – 2.30 (m, 2H), 1.91 – 1.67 (m, 4H), 1.27 – 0.70 (m, 15H), 0.33 – 0.22 (m, 2H).

Example 121

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-

carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **121**

Step 1

3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **121a**

Compound **107h** (500 mg, 1.55 mmol), Compound **94d**(961.26 mg, 1.55 mmol) and cesium carbonate (1.52 g, 4.66 mmol) were dissolved in dioxane (15 mL) and water (5.0 mL). Pd(dtbpf)Cl_2 (101.27 mg, 155.38 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, and the resulting crude product was purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **121a** (200 mg, 376.95 μmol, yield: 24.3%).

MS m/z (ESI): 531.2[M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **121b**

Compound **121a** (70 mg, 131.93 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **121b** (72 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 431.2 [M+1]

Step 3

(1*S*,3*S*,4*R*)-3-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-carbonyl]-5-methylene-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **121c**

Compound **23a**(43.47 mg, 162.61 μmol) and *N,N*-diisopropylethylamine (63.05 mg, 487.84 μmol) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (46.76 mg, 243.92 μmol), HOBT (32.96 mg, 243.92 μmol) and Compound **121b** (70 mg, 162.61 μmol), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with dichloromethane (50 mL), and washed with water (50 mL x 3), and the organic phase was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **121c** (80 mg, 117.69 μmol, yield: 72.4 %).

MS m/z (ESI): 680.2 [M+1]

Step 4

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}imidazo[1,5-*a*]pyridin-8-yl)-*N*-(isopropyl)benzamide **121**

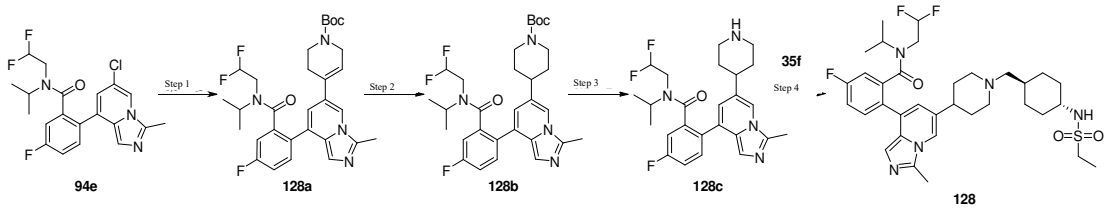
Compound **121c** (80 mg, 117.69 μmol) was dissolved in methane dioxide (3.0 mL) and trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 29%-59%), to obtain the title Compound **121** (17.25 mg, 29.76 μmol, yield: 21.56%) as white solid.

MS m/z (ESI): 580.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 – 8.03 (m, 1H), 7.76 – 7.66 (m, 1H), 7.50 – 7.36 (m, 2H), 7.09 – 6.98 (m, 1H), 6.74 – 6.60 (m, 1H), 6.01 – 5.43 (m, 1H), 4.99 – 4.84 (m, 1H), 4.79 – 4.09 (m, 5H), 4.05 – 3.85 (m, 2H), 3.71 – 3.48 (m, 3H), 2.98 (s, 1H), 2.60 (s, 3H), 2.44 – 2.22 (m, 3H), 1.76 – 1.62 (m, 2H), 1.49 – 1.37 (m, 2H), 0.96 – 0.85 (m, 3H), 0.41 – 0.28 (m, 3H).

Example 128

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]piperidin-4-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **128**



Step 1

4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl formate **128a**

Compound **94e** (365 mg, 890.61 μmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (413.07 mg, 1.34 mmol) and potassium phosphate (567.14 mg, 2.67 mmol) were dissolved in dioxane (8.0 mL) and water (1.0 mL). $Pd(dtbpf)Cl_2$ (58.04 mg, 89.06 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **128a** (450 mg, 808.45 μmol, yield: 90.78%).
MS m/z (ESI): 557.2 [M+1]

Step 2

4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)piperidin-1-tert-butyl formate **128b**

Compound **128a** (450 mg, 808.45 μmol) was dissolved in tetrahydrofuran (10 mL), followed by the addition of Pd/C (86.04 mg, 808.45 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **128b** (300 mg, 537.02 μmol, yield: 66.43%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 559.4 [M+1]

Step 3

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(piperidin-4-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **128c**

Compound **128b** (50 mg, 89.50 μmol) was dissolved in dichloromethane (2.5 mL) and trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. A saturated aqueous sodium carbonate solution (20 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (10 ml×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to obtain the title Compound **128c** (41 mg, 89.42 μmol, yield: 99.9%).
MS m/z (ESI): 459.3 [M+1]

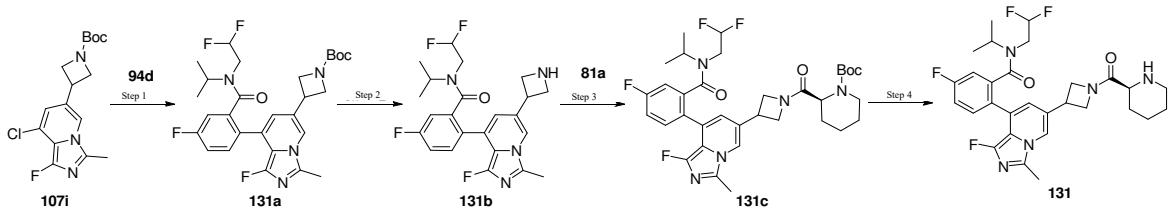
Step 4

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]piperidin-4-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **128**

Compound **128c** (51.24 mg, 89.5 μmol, trifluoroacetate) was dissolved in acetonitrile (2.0 mL), followed by the addition of [(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl4-methylphenyl-1-sulfonate **35f** (67.21 mg, 179.00 μmol), potassium carbonate (61.85 mg, 447.50 μmol) and TBAI(3.31 mg, 8.95 μmol), and the mixture was stirred at 80°C for 12 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, the resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:39%-69%), to obtain the title Compound **128** (27.51 mg, 41.57 μmol, yield: 46.44%) as white solid.
MS m/z (ESI): 662.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.73 – 7.61 (m, 1H), 7.47 – 7.35 (m, 2H), 7.04 – 6.96 (m, 2H), 6.53 (s, 1H), 5.90 – 5.56 (m, 1H), 4.15 – 3.44 (m, 2H), 3.03 – 2.88 (m, 5H), 2.68 – 2.55 (m, 3H), 2.46 – 2.31 (m, 2H), 2.11 – 2.05 (m, 2H), 1.99 (s, 4H), 1.79 – 1.63 (m, 6H), 1.44 – 1.36 (m, 1H), 1.27 – 1.15 (m, 5H), 1.02 – 0.80 (m, 6H), 0.32 – 0.29 (m, 2H).

Example 131

N-(2,2-difluoroethyl)-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-piperidin-2-carbonyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*- (isopropyl)benzamide **131**



Step 1

3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **131a**

Compound **107i** (380 mg, 1.12 mmol), Compound **94d**(1.47 g, 2.57 mmol) and potassium phosphate (712.15 mg, 3.35 mmol) were dissolved in dioxane (8.0 mL) and water (2.0 mL). Pd(dtbpf)Cl_2 (72.89 mg, 111.83 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **131a** (530 mg, 966.15 μmol, yield: 86.4%) as brown solid.
MS m/z (ESI): 549.3[M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-8-yl]-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **131b**

Compound **131a** (130 mg, 236.98 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **131b** (129.4 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 449.2 [M+1]

Step 3

(2*S*)-2-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-carbonyl]piperidin-1-tert-butyl carboxylate **131c**

Compound **81a** (52.24 mg, 227.86 μmol) and DIPEA (88.35 mg, 683.58 μmol) were dissolved in DCM (2 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (52.42 mg, 273.43 μmol) and HOBT (36.95 mg, 273.43 μmol), and the mixture was stirred at room temperature for 0.5 hours. Compound **131b** (102.19 mg, 227.86 μmol) was added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using ethyl acetate/ethanol as an elution system, to obtain the title Compound **131c** (50 mg, 75.79 μmol, yield: 33.26%) as yellow solid.
MS m/z (ESI): 660.3 [M+1]

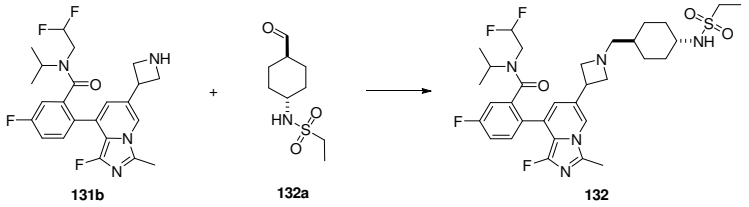
Step 4

N-(2,2-difluoroethyl)-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-piperidin-2-carbonyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **131**

Compound **131c** (50 mg, 75.79 μmol) was dissolved in methane dioxide (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 31%-61%), to obtain the title Compound **131** (12.75 mg, 22.78 μmol, yield: 60.1 %) as yellow solid.
MS m/z (ESI): 560.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.62 – 7.51 (m, 1H), 7.47 – 7.26 (m, 2H), 6.57 – 6.42 (m, 1H), 6.15 – 5.67 (m, 1H), 4.68 – 4.42 (m, 1H), 4.31 – 4.06 (m, 2H), 3.93 – 3.39 (m, 5H), 3.27 – 3.12 (m, 2H), 3.00 – 2.88 (m, 1H), 2.55 (s, 3H), 1.84 – 1.57 (m, 2H), 1.50 – 1.20 (m, 4H), 1.05 – 0.87 (m, 3H), 0.71 – 0.12 (m, 3H).

Example 132

N-(2,2-difluoroethyl)-5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **132**



131b 132a 132

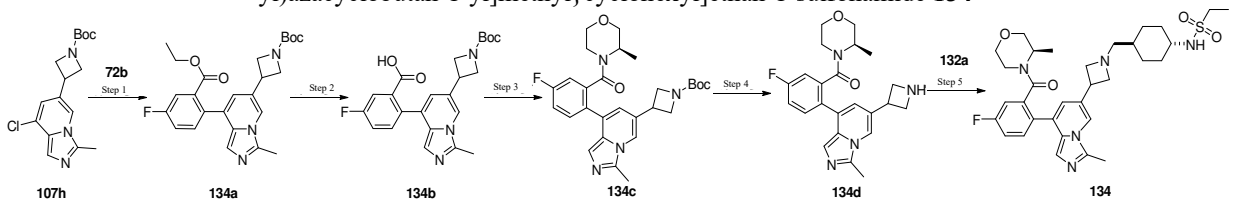
Compound **131b** (129 mg, 229.34 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a** (75.44 mg, 344.01 μmol) and triethylamine (69.62 mg, 688.03 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (43.24 mg, 688.03 μmol) was added, and the mixture was stirred at room temperature for 1.0 hours. A saturated aqueous odium hydrogen carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 39%-69%), to obtain the title Compound **132** (8.73 mg, 13.39 μmol, yield: 5.84 %) as yellow solid.

MS m/z (ESI): 652.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.60 – 7.52 (m, 1H), 7.45 – 7.35 (m, 2H), 7.00 – 6.94 (m, 1H), 6.61 (s, 1H), 6.07 – 5.71 (m, 1H), 3.72 – 3.48 (m, 5H), 3.44 – 3.36 (m, 1H), 3.07 – 2.92 (m, 5H), 2.53 (s, 3H), 2.27 – 2.20 (m, 2H), 1.91 – 1.68 (m, 4H), 1.23 – 1.12 (m, 6H), 0.99 – 0.84 (m, 5H), 0.64 – 0.19 (m, 3H).

Example 134

N-[(1*r*,4*r*)-4-{[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **134**



107h 134a 134b 134c 134d 134

Step 1

3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **134a**

Compound **107h** (300 mg, 932.25 μmol), Compound **72b**(548.40 mg, 1.86 mmol) and cesium carbonate (911.24 mg, 2.80 mmol) were dissolved in dioxane (6.0 mL) and water (1.0 mL). Pd(dtbpf)Cl_2 (60.76 mg, 93.23 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **134a** (415 mg, 915.10 μmol, yield: 98.16%) as yellow oil.

MS m/z (ESI): 454.3[M+1]

Step 2

2-(6-{1-[(tert-butoxy)carbonyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoic acid **134b**

Compound **134a** (375 mg, 826.89 μmol) was dissolved in ethanol (3.0 mL), tetrahydrofuran (3.0 mL) and water (1.5 mL), followed by the addition of LiOH.H_2O (59.41 mg, 2.48 mmol), and stirred at 60°C to allow for reacting for 6.0 hours. The reaction mixture was cooled to room temperature, followed by the addition of a saturated aqueous ammonium chloride solution (10 mL), and the reaction mixture was extracted with ethyl acetate (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The crude product of title Compound **134b** (350 mg, 822.65 μmol, yield: 99.5%) was obtained as yellow oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 426.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.70 – 7.42 (m, 3H), 6.86 (s, 1H), 6.63 (s, 1H), 4.24 (s, 2H), 4.00 – 3.90 (m, 2H), 3.88 – 3.74 (m, 1H), 2.61 (s, 3H), 1.40 (s, 9H).

Step 3

3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **134c**

Compound **134b** (240 mg, 564.11 μmol), (3*R*)-3-methylmorpholine (57.06 mg, 564.11 μmol) and triethylamine (285.41 mg, 2.82 mmol) were dissolved in DMAc (5.0 mL), followed by the addition of HATU (428.98 mg, 1.13

mmol). Under a nitrogen atmosphere, the reaction mixture was stirred at 65°C for 4.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **134c** (240 mg, 471.90 μmol, yield: 83.65%) as yellow oil.

MS m/z (ESI): 509.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 1H), 7.62 (s, 1H), 7.26 – 7.20 (m, 2H), 7.19 – 7.11 (m, 1H), 6.91 – 6.70 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.01 – 3.92 (m, 2H), 3.79 – 3.69 (m, 2H), 2.72 (s, 3H), 2.09 (s, 1H), 2.05 (s, 3H), 1.47 (s, 12H).

Step 4

(3*R*)-4-{2-[6-(azacyclobutan-3-yl)- 3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **134d**

Compound **134c** (130 mg, 255.61 μmol) was dissolved in methane dioxide (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the crude product of title Compound **134d** (104 mg, 254.61 μmol, yield: 99.6%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.4 [M+1]

Step 5

N-[(1*r*,4*r*)-4-{[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **134**

Compound **134d** (104 mg, 254.61 μmol) and triethylamine (62.08 mg, 613.47 μmol) were dissolved in methanol (1.0 mL), and stirred at room temperature for 10 min. The methanol solution (1.0 mL) of *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a** (67.27 mg, 306.73 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (25.70 mg, 408.98 μmol) was added, and the mixture was stirred at room temperature for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 19%-49%), to obtain the title Compound **134** (33.98 mg, 55.54 μmol, yield: 27.2%) as faint yellow solid.

MS m/z (ESI): 612.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.88 (m, 1H), 7.81 – 7.60 (m, 1H), 7.48 – 7.26 (m, 2H), 7.11 – 6.92 (m, 2H), 6.89 – 6.72 (m, 1H), 4.39 – 4.10 (m, 1H), 3.94 – 3.63 (m, 1H), 3.62 – 3.45 (m, 4H), 3.23 – 3.15 (m, 1H), 3.14 – 3.03 (m, 2H), 2.95 (q, J = 7.0 Hz, 4H), 2.88 – 2.66 (m, 1H), 2.60 (s, 3H), 2.25 (d, J = 6.4 Hz, 2H), 1.85 (d, J = 11.2 Hz, 2H), 1.81 – 1.66 (m, 2H), 1.24 – 1.09 (m, 7H), 1.03 (d, J = 6.4 Hz, 1H), 0.98 – 0.83 (m, J = 11.6 Hz, 2H), 0.74 – 0.30 (m, 1H).

Example 136

N-ethyl-5-fluoro-2-[7-methyl-2-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)imidazo[1,5-b]pyridazin-4-yl]-*N*-(isopropyl)benzamide **136**

Step 1

6-{1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}-4-chloropyridazin-3-methyl carboxylate **136b**

4,6-Dichloropyridazin-3-methyl carboxylate **136[a]** (2 g, 9.66 mmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (2.99 g, 9.66 mmol) and sodium carbonate (3.07 g, 28.98 mmol) were

dissolved in dioxane (40 mL) and water (8 mL). Pd (dppf)Cl_2 (706.91 mg, 966.12 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136b** (2.52 g, 7.12 mmol, yield: 73.72%) as yellow oil.
MS m/z (ESI): 354.0 [M+1]
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.33 (br s, 1H), 8.06 (s, 1H), 7.02 (br s, 1H), 6.00 (br s, 1H), 4.13 (br s, 2H), 3.98 (s, 4H), 3.92 (s, 4H), 3.57 (br s, 2H), 3.49 (br s, 1H), 2.67 (br s, 2H), 2.34 (br s, 2H), 1.43 (br s, 17H), 1.06 (s, 8H)

Step 2

6-{1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}-4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyridazin-3-methyl carboxylate **136c**

Compound **136b** (2.5 g, 7.07 mmol), Compound **4c** (3.55 g, 8.48 mmol) and cesium carbonate (6.91 g, 21.20 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). Under a nitrogen atmosphere, Pd(dtbpf)Cl_2 (460.53 mg, 706.61 μmol) was added, and the mixture was stirred at 90°C to allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (100 mL) and extracting with ethyl acetate (100 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136c** (1.38 g, 2.62 mmol, yield: 37.09%).
MS m/z (ESI): 527.3 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 1H), 7.50 (s, 1H), 7.46 – 7.36 (m, 2H), 7.29 (s, 1H), 7.03 (s, 1H), 3.91 (s, 1H), 3.75 – 3.38 (m, 6H), 3.10 (br s, 5H), 2.89 – 2.78 (m, 2H), 1.80 – 1.39 (m, 9H), 0.96 – 0.62 (m, 7H), 0.36 – 0.29 (m, 2H)**.**

Step 3

4-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-6-(hydroxymethyl)pyridazin-3-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136d**

Compound **136c** (1.3 g, 2.47 mmol) was dissolved in tetrahydrofuran (20 mL), and the reaction mixture was cooled to 0°C, followed by the addition of $NaBH_4$ (466.98 mg, 12.34 mmol). The mixture was stirred at room temperature to allow for reacting for 8 hour. The reaction mixture was cooled to 0°C, followed by adding a saturated aqueous ammonium chloride solution (50 mL) and further stirring for 0.5 hours. The reaction mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136d** (545 mg, 1.09 mmol, yield: 44.28%) as reddish orange oil.
MS m/z (ESI): 499.1 [M+1]

Step 4

4-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-6-[(methylsulfonyloxy)methyl]pyridazin-3-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136e**

Compound **136d** (545 mg, 1.09 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (221.22 mg, 2.19 mmol) and methanesulfonic anhydride (228.49 mg, 1.31 mmol). The mixture was stirred at room temperature to allow for reacting for 4.0 hour. The reaction mixture was cooled to 0°C, followed by the addition of a saturated aqueous ammonium chloride solution (20 mL), and the reaction mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **136e** (629 mg, 1.09 mmol, yield: 99.78%) was obtained. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 577.2 [M+1]

Step 5

4-{6-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyridazin-3-yl}-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136f**

The crude product of Compound **136e** (629 mg, 1.09 mmol), 2,3-dihydro-1*H*-isoindol-1,3-dione (192.58 mg, 1.31 mmol) and cesium carbonate (710.76 mg, 2.18 mmol) were dissolved in tetrahydrofuran (15 mL). The reaction mixture was stirred at 65°C to allow for reacting for 12 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136f** (350 mg, 557.59 μmol, yield: 51.12%) as yellow oil.

MS m/z (ESI): 628.3 [M+1]

Step 6

4-[6-(aminomethyl)-5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyridazin-3-yl]-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136g**

Compound **136f** (350 mg, 557.59 μmol) was dissolved in ethanol (10.00 mL), followed by the dropwise addition of hydrazine hydrate (360 mg, 5.75 mmol, 80% purity) while stirring, and the mixture was stirred at 70°C to allow for reacting for 2 hours. The reaction mixture was cooled to 0°C, quenched by adding 1 M aqueous hydrochloric acid solution (20 mL), and stirred for 0.5 hours. The mixture was filtered, and the filter cake was rinsed with a 40% aqueous sodium hydroxide solution. The aqueous phase was extracted with dichloromethane (30 mL x 3), and the organic phases were combined, washed once with saturated aqueous sodium carbonate solution and once with saturated brine, and concentrated under a reduced pressure, to obtain the crude product of title Compound **136g** (236 mg, 474.27 μmol, yield: 85.1%) as yellow oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 498.3 [M+1]

Step 7

4-[6-(acetamidomethyl)-5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}pyridazin-3-yl]-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136h**

The crude product of Compound **136g** (236 mg, 474.27 μmol) and triethylamine (95.98 mg, 948.55 μmol) were dissolved in dichloromethane (10 mL), followed by the dropwise addition of the solution of acetyl chloride (48.40 mg, 616.56 μmol) in dichloromethane (10 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hour. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **136h** (300 mg, 555.93 μmol, yield: 117.22%) as light yellow oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 540.2 [M+1]

Step 8

4-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-7-methylimidazo[1,5-b]pyridazin-2-yl)-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **136i**

The crude product of Compound **136h** (300 mg, 555.93 μmol) was dissolved in dichloromethane (10 mL), followed by the addition of a Burgess reagent (145.73 mg, 611.52 μmol). The mixture was stirred at 40℃ to allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136i** (167 mg, 320.15 μmol, yield: 57.59%) as yellow solid.

MS m/z (ESI): 522.5[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (dd, J = 5.4, 8.5 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.24 (br s, 1H), 6.93 (s, 1H), 6.64 (br s, 1H), 4.09 (br s, 2H), 3.61 – 3.49 (m, 2H), 3.47 – 3.37 (m, 2H), 2.94 – 2.84 (m, 1H), 2.63 (s, 3H), 1.43 (s, 9H), 1.12 – 0.66 (m, 9H), 0.35 (br d, J = 6.3 Hz, 2H).

Step 9

Tert-butyl 4-(4-{2-[ethyl(propan-2-yl)carbamoyl]-4-fluorophenyl}-7-methylimidazo[1,5-b]pyridazin-2-yl)piperidine-1-carboxylate

4-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-7-methylimidazo[1,5-*b*]pyridazin-2-yl)piperidin-1-tert-butyl formate **136j**

Compound **136i** (80 mg, 153.37 μmol) was dissolved in tetrahydrofuran (10 mL), followed by the addition of 50% Pd/C (7.45 mg, 30.67 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through diatomite, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **136j** crude product of (80 mg, 152.78 μmol, yield: 99.6%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 524.2 [M+1]

Step 10

N-ethyl-5-fluoro-2-[7-methyl-2-(piperidin-4-yl)imidazo[1,5-b]pyridazine-4-yl]-N-(propan-2-yl)benzamide

N-ethyl-5-fluoro-2-[7-methyl-2-(piperidin-4-yl)imidazo[1,5-*b*]pyridazin-4-yl]-*N*-(isopropyl)benzamide **136k**

The crude product of Compound **136j** (80 mg, 152.78 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to

obtain the crude product of title Compound **136k** (64 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 424.3 [M+1]

Step 11

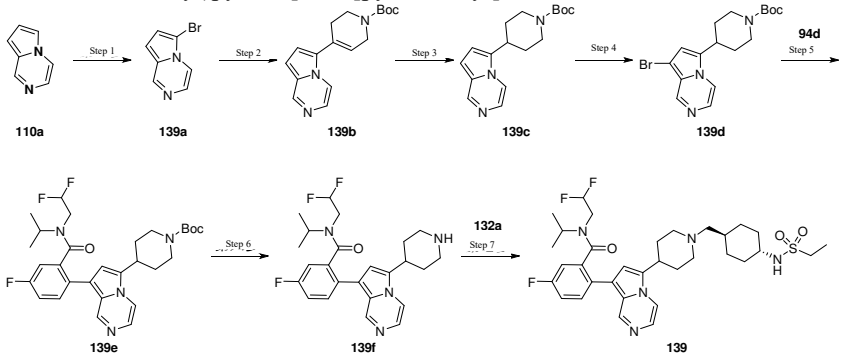
N-ethyl-5-fluoro-2-[7-methyl-2-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)imidazo[1,5-b]pyridazin-4-yl]-N-(propan-2-yl)benzamide

N-ethyl-5-fluoro-2-[7-methyl-2-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)imidazo[1,5-b]pyridazin-4-yl]-*N*-(isopropyl)benzamide **136**

The crude product of Compound **136k** (64 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(41.42 mg, 151.11 μmol) and triethylamine (30.58 mg, 302.23 μmol) were dissolved in methanol (5.0 mL), and stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (28.49 mg, 453.34 μmol) was added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the resulting crude product was purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **136** (18.92 mg, 30.18 μmol, yield: 19.97%) as yellow solid.
MS m/z (ESI): 627.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (dd, J = 5.6, 8.4 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.21 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.58 – 6.52 (m, 1H), 3.48 – 3.38 (m, 1H), 3.03 – 2.92 (m, 5H), 2.85 (m, 1H), 2.69 – 2.62 (m, 1H), 2.61 (s, 3H), 2.15 – 2.04 (m, 2H), 2.02 – 1.92 (m, 2H), 1.91 – 1.81 (m, 4H), 1.80 – 1.70 (m, 4H), 1.43 – 1.34 (m, 1H), 1.23 (s, 3H), 1.21 – 1.15 (m, 4H), 0.95 – 0.91 (m, 3H), 0.91 – 0.84 (m, 2H), 0.84 – 0.77 (m, 3H), 0.40 – 0.35 (m, 2H).

Example 139

N-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)pyrrolo[1,2-*a*]pyrazin-8-yl]benzamide **139**



Step 1

6-bromopyrrolo[1,2-a]pyrazine **139a**

Pyrrolo[1,2-a]pyrazine **110a** (1.0 g, 8.46 mmol) was dissolved in trichloromethane (25 mL), and cooled to -10 °C, followed by the addition of NBS (1.35g, 7.59 mmol). The reaction mixture was stirred at-10 °C for 1.0 hour. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **139a** (1.3 g, 6.60 mmol, yield: 77.94%).
MS m/z (ESI): 198.9[M+1]

Step 2

4-{pyrrolo[1,2-a]pyrazin-6-yl}-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **139b**

Compound **139a** (500 mg, 2.54 mmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (941.60 mg, 3.05 mmol) and sodium carbonate (806.89 mg, 7.61 mmol) were dissolved in dioxane (8 mL) and water (2 mL). Pd (dppf)Cl_2 (185.68 mg, 253.77 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **139b** (750 mg, 2.51 mmol, yield: 98.72%).

MS m/z (ESI): 300.1 [M+1]

Step 3

4-{pyrrolo[1,2-a]pyrazin-6-yl}piperidin-1-tert-butyl carboxylate **139c**

Compound **139b**(750 mg, 2.51 mmol) was dissolved in tetrahydrofuran (20 mL), followed by the addition of Pd/C(300.00 mg, 2.82 mmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (15 psi), and the mixture was stirred at 40°C for 2.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The crude product of title Compound **139c** (700 mg, 2.32 mmol, yield: 92.7%) was obtained.

MS m/z (ESI): 302.2[M+1]

Step 4

4-{8-bromopyrrolo[1,2-a]pyrazin-6-yl}piperidin-1-tert-butyl carboxylate **139d**

Compound **139c** (580 mg, 1.92 mmol) was dissolved in dichloromethane (6.0 mL), followed by the addition of NBS (411.03 mg, 2.31 mmol), and the mixture was stirred at room temperature for 12 hours. NBS (411.03 mg, 2.31 mmol) was supplemented, and the mixture was further stirred for 0.5 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **139d** (272 mg, 715.27 μmol, yield: 37.2%).

MS m/z (ESI): 382.2[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.27 (d, J = 4.9 Hz, 1H), 7.55 (d, J = 5.0 Hz, 1H), 6.95 (s, 1H), 4.15 – 3.96 (m, 3H), 2.89 (s, 3H), 1.90 (d, J = 12.4 Hz, 3H), 1.41 (s, 9H).

Step 5

4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)-piperidin-1-tert-butyl carboxylate **139e**

Compound **139d** (272 mg, 715.27 μmol) and Compound **94d**(885.02 mg, 1.43 mmol) were dissolved in dioxane (8 mL) and water (2.0 mL). Potassium phosphate (455.48 mg, 2.15 mmol) and Pd(dtbpf)Cl_2 (46.62 mg, 71.53 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (10 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **139e** (125 mg, 229.52 μmol, yield: 32.1%).

MS m/z (ESI): 545.4 [M+1]

Step 6

N-(2,2-difluoroethyl)-5-fluoro-2-[6-(piperidin-4-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **139f**

Compound **139e** (125 mg, 229.52 μmol) was dissolved in dichloromethane (4 mL), followed by the addition of trifluoroacetic acid (1.78 g, 15.58 mmol, 1.2 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **139f** (105 mg, 236.22 μmol, yield: 103%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 445.4 [M+1]

Step 7

N-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)-2-[6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)pyrrolo[1,2-*a*]pyrazin-8-yl]benzamide **139**

Compound **139f** (168 mg, 377.96 μmol), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(99.46 mg, 453.55 μmol) and triethylamine (114.74 mg, 1.13 mmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (73.63 mg, 1.17 mmol) was added, and the reaction mixture was stirred at room temperature for 11 hour. Water (5.0 mL) was added to the reaction mixture, which was then extracted with dichloromethane (5 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/ethyl acetate as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 42%-72%), to obtain the title Compound **139** (9.49 mg, 14.65 μmol, yield: 3.88 %) as white solid.

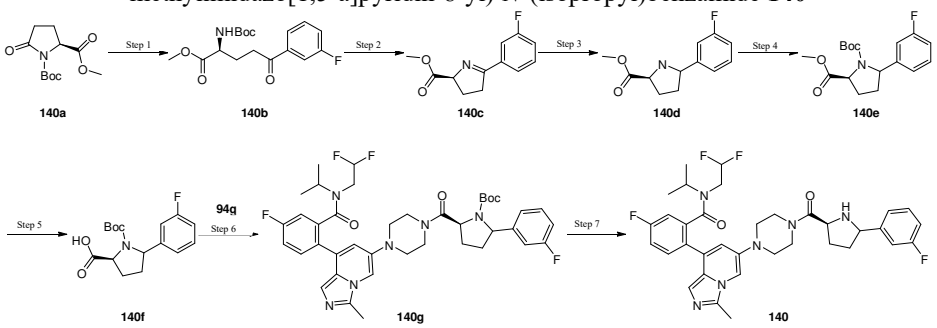
MS m/z (ESI): 648.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.18 (d, J = 4.4 Hz, 1H), 7.65 – 7.49 (m, 2H), 7.42 – 7.29 (m, 2H), 6.99 (d, J = 7.6 Hz, 1H), 6.78 – 6.63 (m, 1H), 6.06 – 5.65 (m, 1H), 3.69 – 3.52 (m, 1H), 3.47 – 3.38 (m, 1H), 3.05 – 2.87 (m, 6H), 2.14 – 2.01 (m, 4H), 1.93 – 1.74 (m, 6H), 1.70 – 1.54 (m, 2H), 1.48 – 1.34 (m, 1H), 1.28 – 1.16 (m,

5H), 1.09 – 0.78 (m, 6H), 0.24 (d, J = 6.8 Hz, 3H).

Example 140

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{4-[(2*S*)-5-(3-fluorophenyl)pyrrolidin-2-carbonyl]piperazin-1-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **140**



Step 1

(2S)-2-{[(tert-butoxy)carbonyl]amino}-5-(3-fluorophenyl)-5-methyl oxopentanoate **104b**

1-Bromo-3-fluorobenzene (4.32 g, 24.69 mmol) was dissolved in THF (42.39 mL), and cooled to 0°C, followed by the dropwise addition of *i*-PrMgCl·LiCl(1.3 M, 18.99 mL), and the reaction mixture was stirred for 1 hour. At -40°C, the above reaction mixture was added to the solution of 2-methyl(2S)-5-oxopyrrolidin-1,2-dicarboxylic acid 1-tert-butyl ester (5 g, 20.57 mmol) in THF (42.39 mL), and the reaction mixture was stirred for 4.0 hours. In an ice bath, a saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **140b** (2.57 g, 7.57 mmol, yield: 36.8%) as oil.

MS m/z (ESI): 240.2 [M-100+1]

Step 2

(2*S*)-5-(3-fluorophenyl)-3,4-dihydro-2*H*-pyrrol-2-methyl carboxylate **140c**

Compound **140b** (300mg, 884.02 μmol) was dissolved in dichloromethane (6.0 mL), and cooled to 0°C, followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL). The reaction mixture was stirred at room temperature for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product of title Compound **140c** (200 mg, 904.05 μmol, yield102.27%) as yellow oil was obtained.

MS m/z (ESI): 222.1 [M+1]

Step 3

(2*S*)-5-(3-fluorophenyl)pyrrolidin-2-methyl carboxylate **140d**

Compound **140c** (200 mg, 904.05 μmol) was dissolved in methanol (2.0 mL), followed by the addition of sodium cyanoborohydride (170.44 mg, 2.71 mmol), and the mixture was stirred at room temperature to allow for reacting for 0.5 hours. The solvent was removed from the reaction mixture under a reduced pressure, followed by the addition of water (10 mL), and the reaction mixture was extracted with ethyl acetate (10ml×3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the crude product of title Compound **140d** (200 mg, 895.89 μmol, yield: 99.1%).

MS m/z (ESI): 224.2 [M+1]

Step 4

2-methyl(2S)-5-(3-fluorophenyl)pyrrolidin-1,2-dicarboxylic acid 1-tert-butyl ester **140e**

Compound **140d** (200 mg, 3.76 mmol) was dissolved in dichloromethane (2.5 mL), followed by the addition of triethylamine (142.78 mg, 1.41 mmol), DMAP(12 mg, 94.07 μmol) and $(Boc)_2$º(307.95 mg, 1.41 mmol), and the mixture was stirred at room temperature to allow for reacting for 2.0 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **104e** (55 mg, 170.09 μmol, yield: 9.04%) as oil.

MS m/z (ESI): 268.2 [M-55]

Step 5

(2*S*)-1-[(tert-butoxy)carbonyl]-5-(3-fluorophenyl)pyrrolidin-2-carboxylic acid **140f**

Compound **140e** (55 mg, 170.09 μmol) was dissolved in methanol (0.2 mL), tetrahydrofuran (0.8 mL) and water (0.2 mL), followed by the addition of $LiOH.H_2O$ (21.41 mg, 510.27 μmol), and the mixture was stirred at room temperature to allow for reacting for 12 hours. The organic solvent was removed from the reaction mixture under a reduced pressure, followed by the addition of 1M aq. HCl (8.0 mL) until the precipitation of white solid, and the

reaction mixture was transferred using 1M HCl and filtered. The filter cake was transferred and dried to subsequently obtain the title Compound **140f** (40 mg, 129.31 μmol, yield: 76.03%).
MS m/z (ESI): 254.0 [M-55]
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 – 12.31 (m, 1H), 7.56 – 7.25 (m, 3H), 7.02 (d, J = 7.8 Hz, 1H), 4.97 – 4.64 (m, 1H), 4.35 – 4.17 (m, 1H), 2.39 – 2.12 (m, 2H), 1.98 – 1.66 (m, 2H), 1.44 – 0.98 (m, 9H).

Step 6

(2*S*)-2-[4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)piperazin-1-carbonyl]-5-(3-fluorophenyl)pyrrolidin-1-tert-butyl carboxylate **140g**

Compound **140f** (40 mg, 129.31 μmol) and DIPEA (116.99 mg, 905.18 μmol) were dissolved in DMF (2.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (37.43 mg, 195.26 μmol), HOBT (26.73 mg, 197.85 μmol) and Compound **94g** (59.42 mg, 129.31 μmol), and the mixture was stirred at room temperature for 12 hours. Water (5 mL) was added to the reaction mixture, which was then extracted with dichloromethane (5 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using ethyl acetate as an elution system, to obtain the title Compound **140g** (17.5 mg, 23.31 μmol, yield: 18.02%).
MS m/z (ESI): 751.4 [M+1]

Step 7

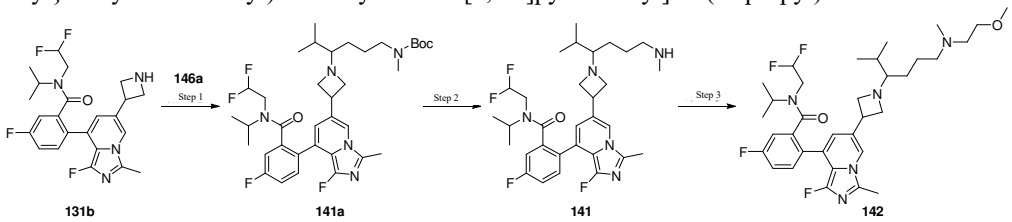
N-(2,2-difluoroethyl)-5-fluoro-2-(6-{4-[(2*S*)-5-(3-fluorophenyl)pyrrolidin-2-carbonyl]piperazin-1-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **140**

Compound **140g** (17.5 mg, 23.31 μmol) was dissolved in methane dioxide (1.0 mL), and cooled to 5°C, followed by the addition of trifluoroacetic acid (444.00 mg, 3.89 mmol, 0.3 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 39%-69%), to obtain the title Compound **140** (4.22 mg, 6.49 μmol, yield: 27.8 %) as yellow solid.
MS m/z (ESI): 651.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 – 7.64 (m, 1H), 7.48 – 7.31 (m, 4H), 7.29 – 7.20 (m, 2H), 7.12 – 6.92 (m, 2H), 6.62 (s, 1H), 5.96 – 5.55 (m, 1H), 4.17 – 4.06 (m, 2H), 3.74 – 3.46 (m, 6H), 3.17 – 2.94 (m, 5H), 2.56 – 2.54 (m, 3H), 2.21 – 2.03 (m, 2H), 2.00 – 1.90 (m, 1H), 1.59 – 1.41 (m, 1H), 0.96 – 0.85 (m, 3H), 0.44 – 0.26 (m, 3H).

Examples 141 and 142

N-(2,2-difluoroethyl)-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[2-methyl-6-(methylamino)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **141**

N-(2,2-difluoroethyl)-5-fluoro-2-[1-fluoro-6-(1-{6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **142**



Step 1

N-{4-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl}-*N*-methyltert-butyl carbamate **141a**

Compound **131b** (81.75 mg, 182.29 μmol) and *N*-methyl-*N*-(5-methyl-4-oxohexyl)tert-butyl carbamate **146a** (66.54 mg, 273.44 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (49.69 mg, 364.58 μmol), and the mixture was stirred at 60°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (34.37 mg, 546.87 μmol) and stirring at 60°C for 2.0 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **141a** (50 mg, 73.99 μmol, yield: 40.59%) as yellow solid.
MS m/z (ESI): 676.5 [M+1]

Step 2

N-(2,2-difluoroethyl)-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[2-methyl-6-(methylamino)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **141**

Compound **141a** (20 mg, 29.59 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of

trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure to obtain a crude product . The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 34%-64%), to obtain the title Compound **141** (4.55 mg, 7.90 μmol, yield: 26.71%).
MS m/z (ESI): 576.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.62 – 7.52 (m, 1H), 7.39 – 7.20 (m, 2H), 6.74 – 6.63 (m, 1H), 6.13 – 5.73 (m, 1H), 3.84 – 3.55 (m, 5H), 3.43 – 3.34 (m, 1H), 3.27 – 3.18 (m, 2H), 2.67 – 2.54 (m, 5H), 2.42 (s, 3H), 2.28 – 2.16 (m, 1H), 1.93 – 1.79 (m, 1H), 1.69 – 1.54 (m, 2H), 1.48 – 1.26 (m, 2H), 1.05 – 0.88 (m, 9H), 0.45 (s, 3H).

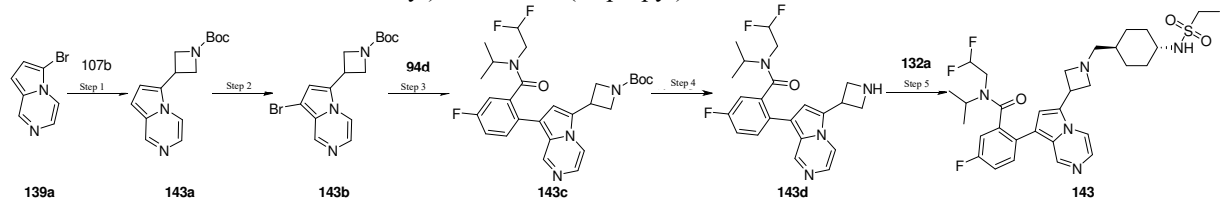
Step 3

N-(2,2-difluoroethyl)-5-fluoro-2-[1-fluoro-6-(1-{6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **142**

Compound **141** (51.04 mg, 74 μmol, trifluoroacetate), 1-bromo-2methoxyethane (20.57 mg, 147.98 μmol), sodium iodide (33.28 mg, 222.00 μmol) and potassium carbonate (61.36 mg, 444.00 μmol) were dissolved in DMF(2.0 mL), and stirred at 50°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 45%-75%), to obtain the title Compound **142** (11.12 mg, 17.55 μmol, yield: 23.71%).
MS m/z (ESI): 634.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.61 – 7.54 (m, 1H), 7.37 – 7.25 (m, 2H), 6.71 (s, 1H), 6.17 – 5.67 (m, 1H), 3.82 – 3.57 (m, 5H), 3.54 – 3.47 (m, 2H), 3.34 – 3.31 (m, 4H), 3.27 – 3.19 (m, 2H), 2.66 – 2.55 (m, 5H), 2.49 – 2.38 (m, 2H), 2.32 – 2.19 (m, 4H), 1.93 – 1.80 (m, 1H), 1.66 – 1.49 (m, 2H), 1.44 – 1.33 (m, 1H), 1.32 – 1.21 (m, 1H), 1.03 – 0.89 (m, 9H), 0.45 (s, 3H).

Example 143

N-(2,2-difluoroethyl)-2-(6-{1-[(4-ethanesulfonamidocyclohexyl)methyl]azacyclobutan-3-yl}pyrrolo[1,2-*a*]pyrazin-8-yl)-5-fluoro-*N*-(isopropyl)benzamide **143**



Step 1

4-{pyrrolo[1,2-a]pyrazin-6-yl}-azacyclobutan-1-tert-butyl carboxylate **143a**

Compound **139a** (500 mg, 2.54 mmol), 3-bromoazacyclobutan-1-tert-butyl carboxylate **107b** (778.90 mg, 3.30 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (28.47 mg, 25.38 μmol), $NiCl_2$.dtbbpy (15.15 mg, 38.06 μmol), tris(trimethylsilyl)silane (631.01 mg, 2.54 mmol) and sodium carbonate (537.93 mg, 5.08 mmol) were dissolved in dimethoxyethane (10 mL), and the reaction mixture was placed under a 10W LED bluelight lamp, and stirred at 25°C to allow for reacting for 14 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were dissolved in ethyl acetate (30 mL), and washed with water (10 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **143a** (299 mg, 1.09 mmol, yield: 43.11%) as yellow oil.
MS m/z (ESI): 274.0 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 7.89 (d, J= 5.2 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.03 (d, J = 4.4 Hz, 1H), 6.98 (d, J = 4.4 Hz, 1H), 4.47 (t, J = 8.4 Hz, 2H), 4.29 – 4.18 (m, 1H), 4.14 – 4.02 (m, 2H), 1.46 (s, 9H).

Step 2

4-{8-bromopyrrolo[1,2-a]pyrazin-6-yl}azacyclobutan-1-tert-butyl carboxylate **143b**

Compound **143a** (199 mg, 728.06 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of NBS (129.58 mg, 728.06 μmol), and the mixture was stirred at room temperature for 3.0 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **143b** (251 mg, 712.61 μmol, yield: 97.88%).
MS m/z (ESI): 354.1[M+1]

Step 3

3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)-azacyclobutan-1-

tert-butyl carboxylate **143c**

Compound **143b** (251 mg, 712.61 μmol) and Compound **94d**(603.93 mg, 1.07 mmol) were dissolved in dioxane (6.0 mL) and water (1.0 mL). Sodium carbonate (226.59 mg, 2.14 mmol) and Pd(dppf)Cl_2 (52.14 mg, 71.26 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **143c** (249 mg, 482.04 μmol, yield: 67.6%).

MS m/z (ESI): 517.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.79 – 8.71 (m, 1H), 7.97 – 7.86 (m, 1H), 7.67 – 7.59 (m, 1H), 7.56 – 7.50 (m, 1H), 7.39 – 7.31 (m, 1H), 7.28 – 7.22 (m, 1H), 7.03 (s, 1H), 6.12 – 5.73 (m, 1H), 4.53 – 4.44 (m, 2H), 4.11 – 4.00 (m, 2H), 3.81 – 3.67 (m, 1H), 3.58 (q, J = 8.8 Hz, 1H), 1.46 (s, 9H), 1.32 – 1.19 (m, 6H), 0.34 (d, J = 6.8 Hz, 2H).

Step 4

2-[6-(azacyclobutan-3-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(2,2-difluoroethyl)-5-fluoro- *N*-(isopropyl)benzamide **143d**

Compound **143c** (50 mg, 96.80 μmol) was dissolved in dichloromethane (5 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **143d** (40 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 417.2 [M+1]

Step 5

N-(2,2-difluoroethyl)-2-(6-{1-[(4-ethanesulfonamidocyclohexyl)methyl]azacyclobutan-3-yl}pyrrolo[1,2-*a*]pyrazin-8-yl)-5-fluoro-*N*-(isopropyl)benzamide **143**

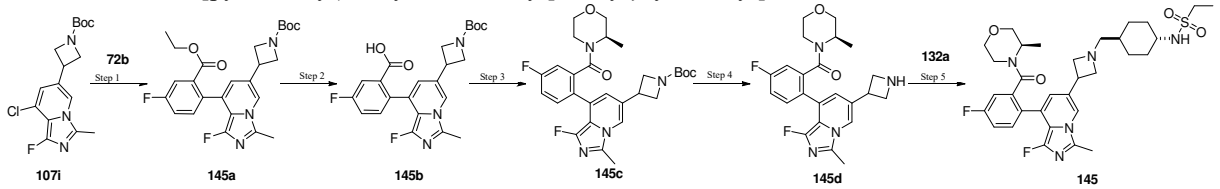
The crude product of Compound **143d** (40 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(14.63 mg, 66.73 μmol) and triethylamine (13.51 mg, 133.47 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hours. Sodium cyanoborohydride (5.59 mg, 88.98 μmol) was added, and the mixture was stirred at room temperature for 11 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **143** (17.36 mg, 28.01 μmol, yield: 63.96%) as yellow solid.

MS m/z (ESI): 620.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.03 – 7.93 (m, 1H), 7.68 – 7.57 (m, 1H), 7.54 – 7.44 (m, 1H), 7.40 – 7.31 (m, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.95 (s, 1H), 6.14 – 5.76 (m, 1H), 4.12 – 4.02 (m, 1H), 3.93 (s, 2H), 3.83 – 3.67 (m, 1H), 3.64 – 3.52 (m, 1H), 3.15 – 3.08 (m, 1H), 3.06 – 2.98 (m, 2H), 2.46 – 2.40 (m, 2H), 2.01 (d, J = 11.6 Hz, 2H), 1.85 (d, J = 11.6 Hz, 2H), 1.36 – 1.28 (m, 8H), 1.13 – 1.01 (m, 3H), 0.98 – 0.94 (m, 3H), 0.91 – 0.83 (m, 1H), 0.39 – 0.28 (m, 3H).

Example 145

N-[(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **145**



Step 1

3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **145a**

Compound **107i** (260 mg, 765.17 μmol), Compound **72b**(450.11 mg, 1.53 mmol) and cesium carbonate (747.93 mg, 2.30 mmol) were dissolved in dioxane (12.0 mL) and water (2.0 mL). Pd(dtbpf)Cl_2 (49.87 mg, 76.52 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **145a** (251 mg, 532.35 μmol, yield: 69.6%) as yellow oil.

MS m/z (ESI): 472.3[M+1]

Step 2

2-(6-{1-[(tert-butoxy)carbonyl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoic acid **145b**

Compound **145a** (251 mg, 532.35 μmol) was dissolved in ethanol (3.0 mL), tetrahydrofuran (3.0 mL) and water (1.5 mL), followed by the addition of $LiOH.H_2O$ (38.25 mg, 1.60 mmol), and stirred at 60°C to allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, followed by the addition of a saturated aqueous ammonium chloride solution (10 mL), the reaction mixture was then extracted with trichloromethane/isopropanol (2: 1; 10 mL×3). The organic phase was concentrated under a reduced pressure. The crude product of title Compound **145b** (236 mg, 532.20 μmol, yield: 99.97%) as yellow solid was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 444.1 [M+1]

Step 3

3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **145c**

Compound **145b** (236 mg, 478.98 μmol), (3*R*)-3-methylmorpholine (53.29 mg, 526.88 μmol) and triethylamine (145.40 mg, 1.44 mmol) were dissolved in DMAc (10 mL), followed by the addition of HATU (364.25 mg, 957.96 μmol). Under a nitrogen atmosphere, the reaction mixture was stirred at 60℃ for 6.0 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **145c** (250 mg, 474.77 μmol, yield: 99.12%) as yellowish green solid.

MS m/z (ESI): 527.2 [M+1]

Step 4

(3*R*)-4-{2-[6-(azacyclobutan-3-yl)-1-fluoro3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **145d**

Compound **145c** (100 mg, 189.91 μmol) was dissolved in methane dioxide (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **145d** (90 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 427.2 [M+1]

Step 5

N-[(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **145**

The crude product of Compound **145d** (90 mg) and triethylamine (57.65 mg, 569.74 μmol) were dissolved in methanol (5.0 mL). *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a** (45.81 mg, 208.90 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (23.87 mg, 379.83 μmol) was added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (20 mL) was added, and the mixture was extracted with ethyl acetate (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 27%-57%), to obtain the title Compound **145** (21.6 mg, 34.30 μmol, yield: 18.1 %) as yellow solid.

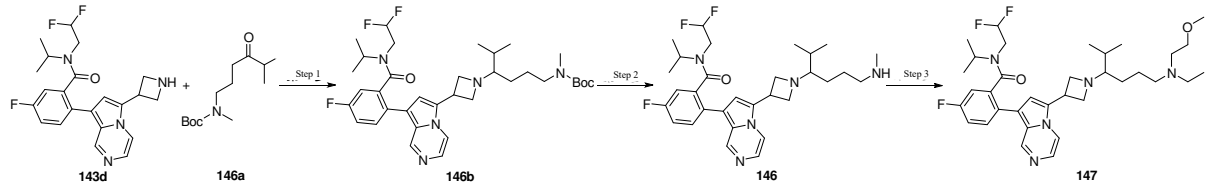
MS m/z (ESI): 630.3[M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 10.8 Hz, 1H), 7.64 – 7.50 (m, 1H), 7.39 – 7.13 (m, 2H), 6.85 – 6.50 (m, 1H), 4.63 – 4.35 (m, 4H), 3.77 – 3.68 (m, 3H), 3.65 – 3.54 (m, 1H), 3.25 – 3.17 (m, 2H), 3.14 – 3.07 (m, 1H), 3.07 – 2.97 (m, 3H), 2.60 (s, 3H), 2.43 (d, J = 6.8 Hz, 2H), 2.04 (s, 1H), 2.02 – 1.96 (m, 2H), 1.89 – 1.80 (m, 2H), 1.37 – 1.26 (m, 7H), 1.23 – 1.13 (m, 1H), 1.11 – 0.98 (m, 2H), 0.86 – 0.71 (m, 1H).

Examples 146 and 147

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[2-methyl-6-(methylamino)hexan-3-yl]azacyclobutan-3-yl}pyrrolo[1,2-a]pyrazin-8-yl)-*N*-(isopropyl)benzamide **146**

N-(2,2-difluoroethyl)-5-fluoro-2-[6-(1-{6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl}azacyclobutan-3-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **147**



Step 1

N-{4-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}pyrrolo[1,2-a]pyrazin-6-yl)azacyclobutan-1-yl]-5-methylhexyl}-*N*-methyltert-butyl carbamate **146b**

Compound **143d** (101 mg, 242.53 μmol) and *N*-methyl-*N*-(5-methyl-4-oxohexyl)tert-butyl carbamate **146a** (64.92 mg, 266.79 μmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (66.11 mg, 485.07 μmol), and the mixture was stirred at 60°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (45.72 mg, 727.60 μmol) and stirring at 60℃ for 13 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **146b** (80 mg, 124.27 μmol, yield: 51.24%) as yellow solid.

MS m/z (ESI): 644.3 [M+1]

Step 2

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[2-methyl-6-(methylamino)hexan-3-yl]azacyclobutan-3-yl}pyrrolo[1,2-a]pyrazin-8-yl)-*N*-(isopropyl)benzamide **146**

Compound **146b** (30 mg, 46.60 μmol) was dissolved in dichloromethane (5.4 mL), followed by the addition of trifluoroacetic acid (888.00 mg, 7.79 mmol, 600.00 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. Ammonia water (5.0 mL) was added to the reaction mixture, which was then concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **146** (2.48 mg, 4.56 μmol, yield: 9.79%).

MS m/z (ESI): 544.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 6.4 Hz, 1H), 7.92 (dd, J = 0.8, 1.2 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.40 (d, J = 5.2 Hz, 1H), 7.25 (q, J = 8.4 Hz, 1H), 7.15 (t, J = 2.8 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H), 6.06 – 5.69 (m, 1H), 3.91 – 3.80 (m, 3H), 3.73 – 3.58 (m, 1H), 3.53 – 3.43 (m, 1H), 2.72 – 2.56 (m, 2H), 2.42 (d, J = 2.8 Hz, 3H), 2.11 – 2.03 (m, 1H), 1.82 – 1.70 (m, 1H), 1.59 – 1.49 (m, 2H), 1.38 – 1.17 (m, 6H), 0.88 – 0.82 (m, 9H), 0.29 – 0.16 (m, 3H).

Step 3

N-(difluoroethyl)-5-fluoro-2-[6-(1-{6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl}azacyclobutan-3-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **147**

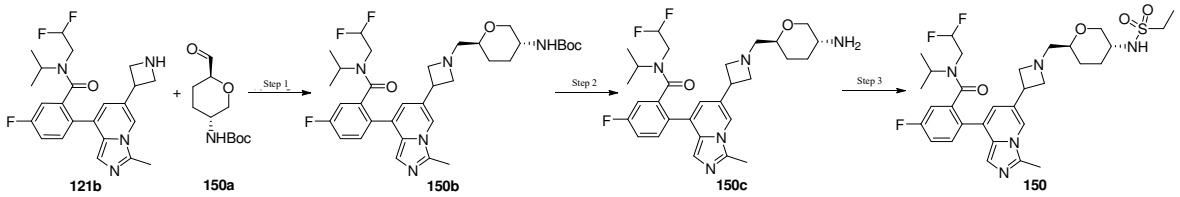
Compound **146** (16 mg, 29.43 μmol), 1-bromo-2methoxyethane (8.18 mg, 58.86 μmol), sodium iodide (13.23 mg, 88.29 μmol) and potassium carbonate (24.40 mg, 176.58 μmol) were dissolved in DMF(1.0 mL), and stirred at 50 ℃ to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 40%-70%), to obtain the title Compound **147** (8.18 mg, 13.59 μmol, yield: 46.2%).

MS m/z (ESI): 602.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.90 – 7.76 (m, 1H), 7.46 – 7.39 (m, 1H), 7.35 – 7.28 (m, 1H), 7.16 (q, J = 8.4 Hz, 1H), 7.10 – 7.00 (m, 1H), 6.75 (d, J = 6.0 Hz, 1H), 5.95 – 5.62 (m, 1H), 3.84 – 3.69 (m, 3H), 3.64 – 3.48 (m, 1H), 3.40 (q, J = 8.8 Hz, 1H), 3.32 (d, J = 11.2 Hz, 2H), 3.14 (s, 3H), 3.12 – 3.01 (m, 3H), 2.42 (d, J = 11.2 Hz, 2H), 2.28 – 2.19 (m, 2H), 2.10 (d, J = 1.2 Hz, 3H), 2.02 – 1.94 (m, 1H), 1.76 – 1.62 (m, 1H), 1.45 – 1.33 (m, 2H), 1.27 – 1.05 (m, 2H), 0.80 – 0.72 (m, 9H), 0.22 – 0.06 (m, 3H).

Example 150

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluoro-*N*-(isopropyl)benzamide **150**



Step 1

N-[(3*R*,6*S*)-6-{[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}oxacyclohexan-3-yl]tert-butyl carbamate **150b**

Compound **121b** (97.36 mg, 226.17 μmol), *N*-[(3*R*,6*S*)-6-formyloxacyclohexan-3-yl]tert-butyl carbamate **150a** (57.04 mg, 248.79 μmol) and triethylamine (45.77 mg, 452.34 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 20 min. Sodium cyanoborohydride (42.64 mg, 678.51 μmol) was added, and the mixture was stirred at room temperature for 0.5 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **150b** (120 mg, 186.41 μmol, yield: 82.4%) as yellow oil.

MS m/z (ESI): 644.4 [M+1]

Step 2

2-[6-(1-{[(2*S*,5*R*)-5-aminooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(2,2-difluoroethyl)-5-fluoro-(isopropyl)benzamide **150c**

Compound **150b** (120 mg, 186.41 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **150c** (105 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 544.3 [M+1]

Step 3

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluoro-*N*-(isopropyl)benzamide **150**

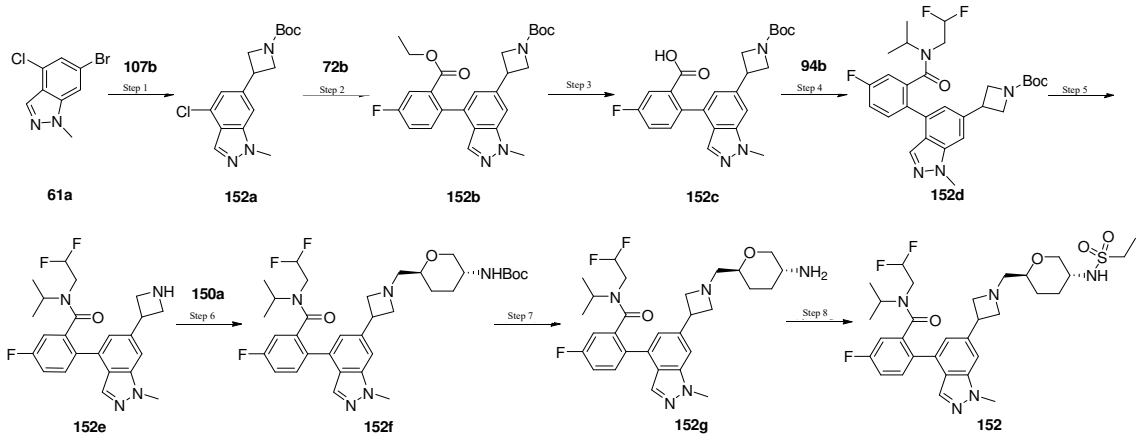
The crude product of Compound **150c** (100 mg) was dissolved in dichloromethane (2.5 mL), followed by the addition of triethylamine (51.48 mg, 508.78 μmol), cooling to 0°C, and the slow dropwise addition of ethanesulfonyl chloride (32.71 mg, 254.39 μmol), and the mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title Compound **150** (16.99 mg, 26.72 μmol, yield: 15.76 %) as white solid.

MS m/z (ESI): 636.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.74 – 7.63 (m, 1H), 7.49 – 7.34 (m, 2H), 7.13 – 6.97 (m, 2H), 6.75 (s, 1H), 5.96 – 5.56 (m, 1H), 3.82 (s, 1H), 3.66 – 3.49 (m, 5H), 3.22 – 3.09 (m, 4H), 3.05 – 2.95 (m, 3H), 2.60 – 2.56 (m, 3H), 2.48 – 2.39 (m, 2H), 1.94 (s, 1H), 1.75 – 1.63 (m, 1H), 1.45 – 1.14 (m, 6H), 0.90 (s, 3H), 0.32 (s, 3H).

Example 152

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-5-fluoro-*N*-(isopropyl)benzamide **152**



Step 1

3-(4-chloro-1-methyl-1*H*-indazol-6-yl) azacyclobutan-1-tert-butyl carboxylate **152a**

Compound **61a** (4.5 g, 18.33 mmol), 3-bromoazacyclobutan-1-tert-butyl carboxylate **107b**(5.63 g, 23.83 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)$ (PF_6)(206 mg, 184 μmol), $NiCl_2$.dtbbpy (109.5 mg, 275 μmol), tris(trimethylsilyl)silane (4.56 g, 18.33 mmol) and sodium carbonate (3.89 g, 36.66 mmol) were dissolved in dimethoxyethane (320 mL), and the reaction mixture was placed under a 10W LED bluelight lamp, and stirred at 25°C to allow for reacting for 3.0 hours. The reaction mixture was filtered, the filter cake was washed with ethyl acetate, the filtrate was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **152a** (3.75 g, 11.65 mmol, yield: 63.6%) as brown oil.

MS m/z (ESI): 321.9 [M+1]

Step 2

3-{4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}azacyclobutan-1-tert-butyl carboxylate **152b**

Compound **152a** (2 g, 4.47 mmol), Compound **72b**(1.97 g, 6.71 mmol) and potassium phosphate (2.85 g, 13.42 mmol) were dissolved in dioxane (24.0 mL) and water (3.0 mL). $Pd(dtbpf)Cl_2$ (291.64 mg, 447.48 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **152b** (1.90 g, 4.19 mmol, yield: 93.6%) as yellow oil.

MS m/z (ESI): 454.1[M+1]

^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.45 (dd, J = 5.6, 8.3 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.01 – 6.97 (m, 1H), 4.41 (t, J = 8.6 Hz, 2H), 4.16 – 4.11 (m, 1H), 4.10 (s, 3H), 4.07 (br d, J = 8.4 Hz, 2H), 3.96 – 3.87 (m, 1H), 3.40 (d, J = 15.2 Hz, 1H), 1.48 (s, 9H), 1.25 (s, 3H).

Step 3

2-(6-{1-[(tert-butoxy)carbonyl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluorobenzoic acid **152c**

Compound **152b** (1.9 g, 4.19 mmol) was dissolved in ethanol (12 mL), tetrahydrofuran (12 mL) and water (6.0 mL), followed by the addition of $LiOH.H_2O$ (301.00 mg, 12.57 mmol), and the mixture was stirred at 50°Cto allow for reacting for 5.0 hours. The mixture was cooled to room temperature, followed by removing the organic solvent under a reduced pressure. The mixture was regulated to PH = 7 by adding 1M HCl, and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **152c** (1.62 g, 3.81 mmol, yield: 90.89%) as tan solid was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 426.1 [M+1]

Step 4

3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-tert-butyl carboxylate **152d**

Compound **152c** (300 mg, 705.13 μmol), Compound **94b** (168.81 mg, 1.06 mmol, hydrochloride) and 2-chloro-1-methylpyridinium iodide (234.19 mg, 916.67 μmol) were dissolved in DMF(3.0 mL), followed by the addition of DIPEA(273.4 mg, 2.12 mmol). The reaction mixture was stirred at room temperature for 12 hours. Ethyl acetate (20 mL) was added to the reaction mixture, which was then washed with water (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to

obtain the title Compound **152d** (317 mg, 597.46 μmol, yield: 84.7%) as yellow solid.
MS m/z (ESI): 531.2 [M+1]

Step 5

2-[6-(azacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **152e**

Compound **152d** (110 mg, 207.32 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **152e** (89 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 431.2 [M+1]

Step 6

N-[(3*R*,6*S*)-6-{[3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}oxacyclohexan-3-yl]tert-butyl carbamate **152f**

The crude product of Compound **152e** (89 mg), *N*-[(3*R*,6*S*)-6-formyloxacyclohexan-3-yl]tert-butyl carbamate **150a** (56.88 mg, 248.10 μmol) and triethylamine (62.76 mg, 620.26 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (25.99 mg, 413.51 μmol) was added, and the mixture was stirred at room temperature for 1.0 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **152f** (80 mg, 124.27 μmol, yield: 60.1%) as yellow oil.
MS m/z (ESI): 644.4 [M+1]

Step 7

2-[6-(1-{[(2*S*,5*R*)-5-aminooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-(2,2-difluoroethyl)-5-fluoro-(isopropyl)benzamide **152g**

Compound **152f** (100 mg, 155.34 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **152g** (84 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 544.2 [M+1]

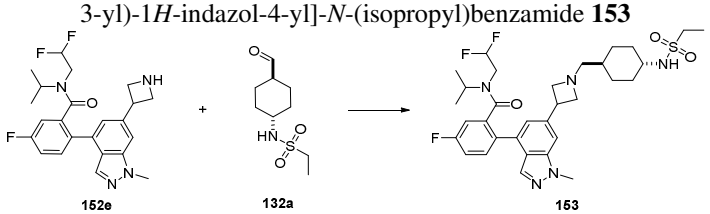
Step 8

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}azacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-5-fluoro-*N*-(isopropyl)benzamide **152**

The crude product of Compound **152g** (84 mg) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (46.91 mg, 463.56 μmol), cooling to 0°C, and the slow dropwise addition of ethanesulfonyl chloride (23.84 mg, 185.42 μmol), and the mixture was stirred at room temperature for 13 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-63%), to obtain the title Compound **152** (20.32 mg, 31.96 μmol, yield: 20.69 %) as white solid.
MS m/z (ESI): 636.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.70 – 7.59 (m, 1H), 7.52 (s, 1H), 7.42 – 7.33 (m, 1H), 7.30 – 7.21 (m, 1H), 7.09 (d, J = 6.0 Hz, 1H), 5.91 – 5.54 (m, 1H), 4.09 (s, 3H), 4.04 – 3.97 (m, 1H), 3.96 – 3.84 (m, 3H), 3.70 – 3.50 (m, 2H), 3.40 – 3.33 (m, 3H), 3.29 – 3.16 (m, 2H), 3.16 – 3.09 (m, 1H), 3.05 (q, J = 7.4 Hz, 2H), 2.67 – 2.58 (m, 2H), 2.15 – 2.01 (m, 1H), 1.75 – 1.66 (m, 1H), 1.56 – 1.34 (m, 2H), 1.31 (t, J = 7.4 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.13 (d, J = 6.8 Hz, 3H).

Example 153

N-(2,2-difluoroethyl)-5-fluoro-2-[1-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}-azacyclobutan-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **153**

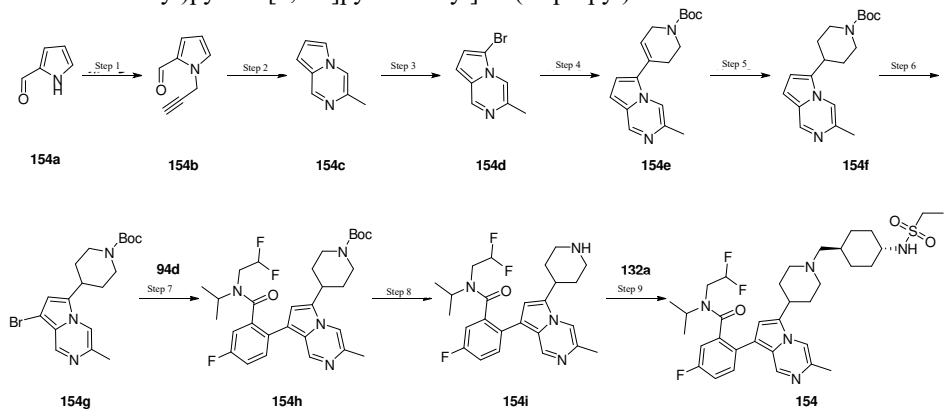


Compound **152e** (56.79 mg, 104.30 μmol, trifluoroacetate), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a** (25.16 mg, 114.73 μmol) and triethylamine (31.66 mg, 312.90 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hours. Sodium cyanoborohydride (13.11 mg, 208.60 μmol) was added, and the

mixture was stirred at room temperature for 1.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/tetrahydrofuran as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 38%-68%), to obtain the title Compound **153** (9.62 mg, 15.18 μmol, yield: 14.55 %) as white solid.
MS m/z (ESI): 634.3 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, J = 0.8 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.39 (s, 1H), 7.30 – 7.22 (m, 1H), 7.16 (dd, J = 2.6, 8.8 Hz, 1H), 6.97 (d, J = 0.8 Hz, 1H), 5.83 – 5.40 (m, 1H), 3.97 (s, 3H), 3.86 – 3.76 (m, 1H), 3.76 – 3.68 (m, 2H), 3.61 – 3.30 (m, 2H), 3.16 – 2.95 (m, 4H), 2.95 – 2.86 (m, 2H), 2.32 (d, J = 6.8 Hz, 2H), 1.94 – 1.85 (m, 2H), 1.81 – 1.70 (m, 2H), 1.34 – 1.13 (m, 7H), 1.01 – 0.86 (m, 3H), 0.78 (d, J = 6.4 Hz, 3H), 0.01 (d, J = 6.4 Hz, 2H).

Example 154

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)pyrrolo[1,2-*a*]pyrazin-8-yl]-*N*-(isopropyl)benzamide **154**



Step 1

1-(prop-2-yn-1-yl)-1*H*-pyrrol-2-formaldehyde **154b**

1*H*-pyrrol-2-formaldehyde **154a** (5.0 g, 52.58 mmol) was dissolved in DMF (40 mL), and cooled to 0 °C, followed by the slow addition of sodium hydride (2.52 g, 63.09 mmol, 60%purity), and the mixture was stirred for 0.5 hours. 3-Bromoprop-1-yne (9.38 g, 63.09 mmol) was dissolved in DMF (30 mL), and then slowly dropwise added to the above reaction mixture. The resulting reaction mixture was slowly warmed to room temperature, and stirred to allow for reacting for 12 hours. In an ice-water bath, a saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with water (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **154b** (3.3 g, 24.78 mmol, yield: 47.14%).
MS m/z (ESI): 134.3[M+1]
^{1}H NMR (400 MHz, CDCl3) δ 9.56 (d, *J* = 0.9 Hz, 1H), 7.27 (s, 1H), 6.97 (dd, *J* = 1.7, 4.1 Hz, 1H), 6.29 (dd, *J* = 2.6, 4.0 Hz, 1H), 5.21 (d, *J* = 2.5 Hz, 2H), 2.47 (t, *J* = 2.6 Hz, 1H).

Step 2

3-methylpyrrolo[1,2-a]pyrazine **154c**

Compound **154b** (3 g, 22.53 mmol) was dissolved in DMF (30 mL), followed by the addition of ammonium acetate (2.08 g, 27.05 mmol) and DBU (3.44 g, 22.56 mmol). The reaction mixture was stirred at80 ℃ for 12 hour. Water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (35 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **154c** (1.3 g, 9.84 mmol, yield: 43.66%) as brown solid.
MS m/z (ESI): 133.1[M+1]

Step 3

6-bromo-3-methylpyrrolo[1,2-a]pyrazine **154d**

Compound **154c** (1.0 g, 7.57 mmol) was dissolved in trichloromethane (25 mL), and cooled to -10°C, followed by the addition of NBS (1.22 g, 6.85 mmol). The reaction mixture was stirred at-10 °C for 1.0 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography

using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **154d** (700 mg, 3.32 mmol, yield: 43.83%) as brown solid.
MS m/z (ESI): 213.0[M+1]

Step 4

4-{3-methylpyrrolo[1,2-a]pyrazin-6-yl}-1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate **154e**

Compound **154d** (500 mg, 2.37 mmol), 4-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,6-tetrahydropyridin-1-tert-butyl carboxylate (879.02 mg, 2.84 mmol) and sodium carbonate (753.27 mg, 7.11 mmol) were dissolved in dioxane (10 mL) and water (2 mL). Pd (dppf)Cl_2 (173.34 mg, 236.90 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **154e** (600 mg, 1.91 mmol, yield: 80.82%).
MS m/z (ESI): 314.2 [M+1]

Step 5

4-{3-methylpyrrolo[1,2-a]pyrazin-6-yl}piperidin-1-tert-butyl carboxylate **154f**

Compound **154e** (600 mg, 1.91 mmol) was dissolved in tetrahydrofuran (20 mL), followed by the addition of 10% Pd/C (257.14 mg, 241.63 μmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (15 psi), and the mixture was stirred at room temperature for 12.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The crude product of title Compound **154f** (590 mg, 1.87 mmol, yield: 97.7%) was obtained. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 316.0[M+1]

Step 6

4-{8-bromo-3-methylpyrrolo[1,2-a]pyrazin-6-yl}piperidin-1-tert-butyl carboxylate **154g**

Compound **154f** (590 mg, 1.87 mmol) was dissolved in dichloromethane (20 mL), followed by the addition of NBS (400 mg, 2.25 mmol), and the mixture was stirred at room temperature for 1.0 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **154g** (425 mg, 1.08 mmol, yield: 57.6%) as brown solid.
MS m/z (ESI): 394.1[M+1]

Step 7

4-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylpyrrolo[1,2-a]pyrazin-6-yl)-piperidin-1-tert-butyl carboxylate **154h**

Compound **154g** (300 mg, 760.83 μmol) and Compound **94d** (282.42 mg, 760.83 μmol) were dissolved in dioxane (5 mL) and water (1.0 mL). Potassium phosphate (484.50 mg, 2.28 mmol) and Pd(dtbpf)Cl_2 (49.59 mg, 76.08 μmol) were added, and the mixture was stirred at 95 °C under a nitrogen atmosphere to allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **154h** (150 mg, 268.51 μmol, yield: 35.3%).
MS m/z (ESI): 559.3 [M+1]

Step 8

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(piperidin-4-yl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **154i**

Compound **154h** (130 mg, 232.71 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0℃. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **154i** (110 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 459.3 [M+1]

Step 9

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(1-{[(1r,4r)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-4-yl)pyrrolo[1,2-*a*]pyrazin-8-yl]-*N*-(isopropyl)benzamide **154**

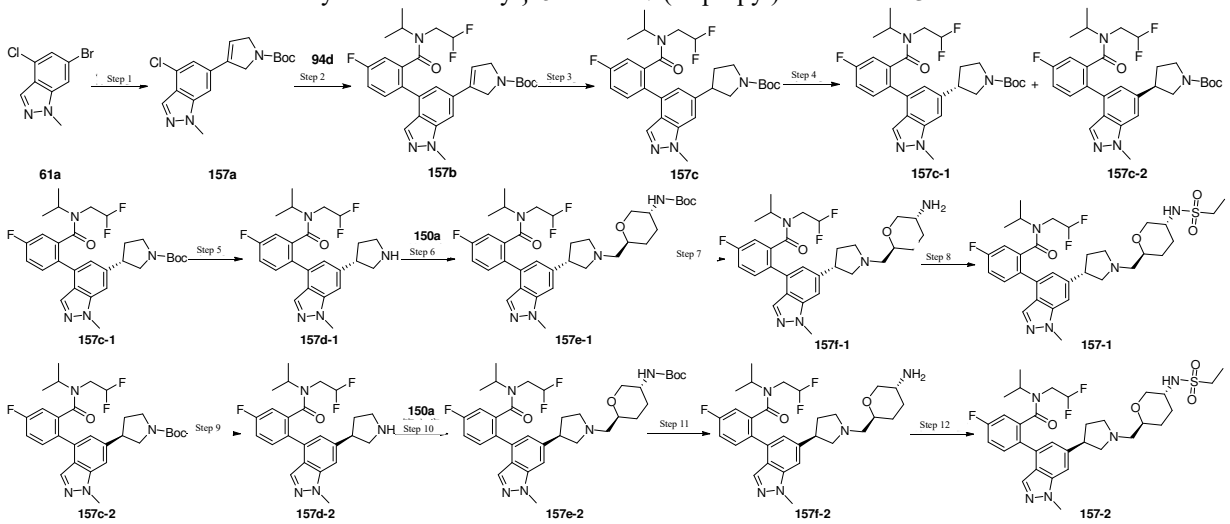
The crude product of Compound **154i** (110 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(50.56 mg, 230.55 μmol) and triethylamine (38.88 mg, 384.25 μmol) were dissolved in methanol (2.0 mL), and stirred at room

temperature for 0.5 hours. Sodium cyanoborohydride (36.22 mg, 576.38 μmol) was added, and the mixture was stirred at room temperature for 2.0 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 42%-72%), to obtain the title Compound **154** (16.56 mg, 25.02 μmol, yield: 13.02 %) as white solid.
MS m/z (ESI): 662.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 – 8.57 (m, 1H), 8.02 (s, 1H), 7.65 – 7.51 (m, 1H), 7.43 – 7.17 (m, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.12 – 5.70 (m, 1H), 3.69 – 3.50 (m, 1H), 3.48 – 3.32 (m, 2H), 3.20 – 2.85 (m, 6H), 2.34 (s, 3H), 2.18 – 1.98 (m, 4H), 1.97 – 1.71 (m, 6H), 1.69 – 1.50 (m, 2H), 1.48 – 1.33 (m, 1H), 1.30 – 0.17 (m, 13H).

Examples 157-1 and 157-2

N-(2,2-difluoroethyl)-2-{6-[(3*S*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-5-fluoro-*N*-(isopropyl)benzamide **157-1**

N-(2,2-difluoroethyl)-2-{6-[(3*R*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-5-fluoro-*N*-(isopropyl)benzamide **157-2**



Step 1

3-{4-chloro-1-methyl-1*H*-indazol-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **157a**

Compound **61a** (1 g, 4.07 mmol) was dissolved in dioxane (6.0 mL) and water (1.0 mL). Sodium carbonate (1.30 g, 12.22 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (1.32 g, 4.48 mmol) and Pd(dppf)Cl_2(298.04 mg, 407.33 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (100 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **157a** (1.35 g, 4.04 mmol, yield: 99.29%) as yellow solid.
MS m/z (ESI): 334.1 [M+1]

Step 2

3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **157b**

Compound **157a** (500 mg, 1.50 mmol) and Compound **94d** (1.11 g, 3.00 mmol) were dissolved in dioxane (8.0 mL) and water (1.0 mL). Potassium phosphate (881.35 mg, 3.74 mmol) and Pd(dtbpf)Cl_2 (97.62 mg, 149.78 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **157b** (800 mg, 1.47 mmol, yield: 98.4%) as yellow oil.
MS m/z (ESI): 543.3 [M+1]

Step 3

3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate **157c**

Compound **157b** (800 mg, 1.47 mmol) was dissolved in methanol (15.0 mL), followed by the addition of Pd/C (17.46 mg, 147.44 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 26 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **157c** (800 mg, 1.47 mmol, yield: 99.6%).

MS m/z (ESI): 545.3 [M+1]

Step 4

(3*S*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate **157c-1**

(3*R*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-tert-butyl formate **157c-2**

Compound **157c** (800 mg, 1.47 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IK (250 mm * 30 mm, 10 um), mobile phase: 20% - 20% (v/v) carbon dioxide-methanol (0.1% ammonia water)), to obtain the title Compounds **157c-1** (110 mg, 201.98 μmol, yield: 13.75%) and **157c-2** (156 mg, 286.45 μmol, yield: 19.5%).

Single-configuration Compound 157c-1:

MS m/z (ESI):545.3 [M+1]

SFC analysis: retention time: 1.318 min; chromatographic column: Chiralpak IK-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 157c-2:

MS m/z (ESI):545.3 [M+1]

SFC analysis: retention time: 1.235 min; chromatographic column: Chiralpak IK-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

Steps 5 and 9

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(3*S*)-pyrrolidin-3-yl]-1*H*-indazol-5-yl}-*N*-(isopropyl)benzamide **157d-1**

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(3*R*)-pyrrolidin-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **157d-2**

Compound **157c-1/157c-2** (50 mg/50 mg, 91.81 μmol/91.81 μmol) was dissolved in methane dioxide (3.0 mL/5.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **157d-1/157d-2** (40.81 mg/40.81 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 157d-1:

MS m/z (ESI): 445.1 [M+1]

Single-configuration Compound 157d-2:

MS m/z (ESI): 445.1 [M+1]

Steps 6 and 10

N-[(3*R*,6*S*)-6-{[(3*S*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}oxacyclohexan-3-yl]tert-butyl carbamate **157e-1**

N-[(3*R*,6*S*)-6-{[(3*R*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]methyl}oxacyclohexan-3-yl]tert-butyl carbamate **157e-2**

The crude product of Compound **157d-1/157d-2** (40.81 mg/40.81 mg) was dissolved in methanol (2.0 mL /2.0 mL), followed by the addition of triethylamine (27.87 mg/27.87 mg, 275.44 μmol/275.44 μmol) and Compound **150a** (25.26 mg/25.26 mg, 110.18 μmol/110.18 μmol), and the mixture was stirred at room temperature for (1.0/1.0) hour. Sodium cyanoborohydride (11.54 mg / 11.54 mg, 183.63 μmol/183.63 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for (13/12) hours. An aqueous sodium bicarbonate solution (20 mL/20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3/10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **157e-1/157e-2** (30 mg/40 mg, 45.61 μmol/60.81 μmol, yield: 49.7%/66.2%)

Single-configuration Compound 157e-1:

MS m/z (ESI):658.3 [M+1]

Single-configuration Compound 157e-2:

MS m/z (ESI):658.3 [M+1]

Steps 7 and 11

2-{6-[(3*S*)-1-{[(2*S*,5*R*)-5-aminooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **157f-1**

2-{6-[(3*R*)-1-{[(2*S*,5*R*)-5-aminooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **157f-2**

Compound **157e-1**/**157e-2** (30 mg/40 mg, 45.61 μmol/60.81 μmol) was dissolved in methane dioxide (5.0 mL/5.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **157f-1**/**157f-2** (25 mg/33.9 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 157f-1:

MS m/z (ESI): 558.5 [M+1]

Single-configuration Compound 157f-1:

MS m/z (ESI): 558.5 [M+1]

Steps 8 and 12

N-(2,2-difluoroethyl)-2-{6-[(3*S*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-5-fluoro-*N*-(isopropyl)benzamide **157-1**

N-(2,2-difluoroethyl)-2-{6-[(3*R*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]-1-methyl-1*H*-indazol-4-yl}-5-fluoro-*N*-(isopropyl)benzamide **157-2**

The crude product of Compound **157f-1**/**157f-2** (25 mg/33.9 mg) was dissolved in dichloromethane (5.0 mL/5.0 mL), followed by the addition of ethanesulfonyl chloride (9.6 mg/12.98 mg, 74.5 μmol/100.94 μmol) and triethylamine (11.3 mg/15.32, 111.7 μmol/151.4 μmol), and the mixture was stirred at room temperature for 12 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system/by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 0%-30%), to obtain the title Compound **157-1**/**157-2** (16.86 mg/11.58 mg, 25.95 μmol/17.82 μmol, yield: 69.71%/35.31%).

Single-configuration Compound 157-1:

MS m/z (ESI):650.4 [M+1]

Chiral SFC: retention time: 2.948 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 30%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.63 (dd, J = 5.4, 8.6 Hz, 1H), 7.53 (s, 1H), 7.38 (dt, J = 2.6, 8.6 Hz, 1H), 7.27 (dd, J = 2.6, 8.8 Hz, 1H), 7.11 (s, 1H), 5.90 – 5.53 (m, 1H), 4.08 (s, 3H), 4.06 – 3.99 (m, 1H), 3.68 – 3.53 (m, 3H), 3.52 – 3.43 (m, 1H), 3.28 – 3.22 (m, 2H), 3.20 – 3.14 (m, 1H), 3.08 – 2.98 (m, 3H), 2.89 – 2.79 (m, 1H), 2.73 – 2.61 (m, 2H), 2.44 – 2.32 (m, 1H), 2.22 – 2.07 (m, 1H), 2.05 – 1.94 (m, 1H), 1.82 – 1.73 (m, 1H), 1.55 – 1.40 (m, 2H), 1.31 (t, J = 7.2 Hz, 5H), 0.90 (d, J = 6.4 Hz, 3H), 0.14 (d, J = 6.4 Hz, 3H).

Single-configuration Compound 157-2:

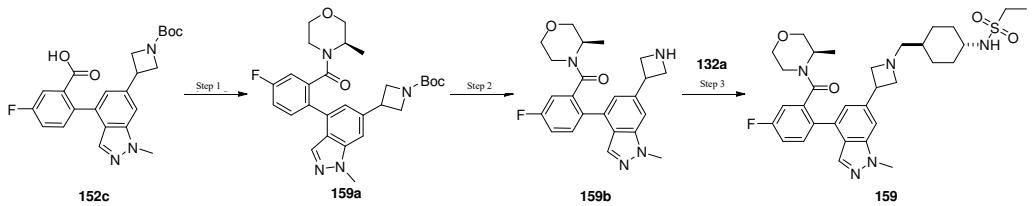
MS m/z (ESI):650.4 [M+1]

Chiral SFC: retention time: 2.154 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 30%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.63 (t, J = 5.2 Hz, 1H), 7.52 (d, J = 3.6 Hz, 1H), 7.37 (td, J = 4.2, 8.2 Hz, 1H), 7.26 (dd, J = 2.6, 8.8 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 5.93 – 5.55 (m, 1H), 4.08 (s, 3H), 4.05 – 3.98 (m, 1H), 3.62 – 3.45 (m, 4H), 3.29 – 3.23 (m, 2H), 3.19 – 3.12 (m, 1H), 3.08 – 2.97 (m, 3H), 2.87 – 2.77 (m, 1H), 2.72 – 2.59 (m, 2H), 2.45 – 2.31 (m, 1H), 2.23 – 2.07 (m, 1H), 2.05 – 1.94 (m, 1H), 1.81 – 1.73 (m, 1H), 1.57 – 1.42 (m, 2H), 1.31 (t, J = 7.4 Hz, 5H), 0.90 (d, J = 6.8 Hz, 3H), 0.19 – 0.06 (m, 3H).

Example 159

N-[(1*r*,4*r*)-4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **159**



Step 1

3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-tert-butyl carboxylate **159a**

Compound **152c** (100 mg, 235.04 μmol), triethylamine (71.35 mg, 705.13 μmol) and HATU(178.74 mg, 470.09 μmol) were dissolved in dichloromethane (2.0 mL), and stirred at room temperature for 10 min, followed by the addition of (3*R*)-3-methylmorpholine (26.15 mg, 258.55 μmol). The reaction mixture was stirred at 50°C for 2 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **159a** (100 mg, 196.62 μmol, yield: 63.7%).

MS m/z (ESI): 453.2 [M-55]

Step 2

6-(azacyclobutan-3-yl)-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **159b**

Compound **159a** (60 mg, 117.97 μmol) was dissolved in dichloromethane (3.4 mL), followed by the addition of trifluoroacetic acid (888.00 mg, 7.79 mmol, 600.00 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **159b** (55 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.3 [M+1]

Step 3

N-[(1*r*,4*r*)-4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **159**

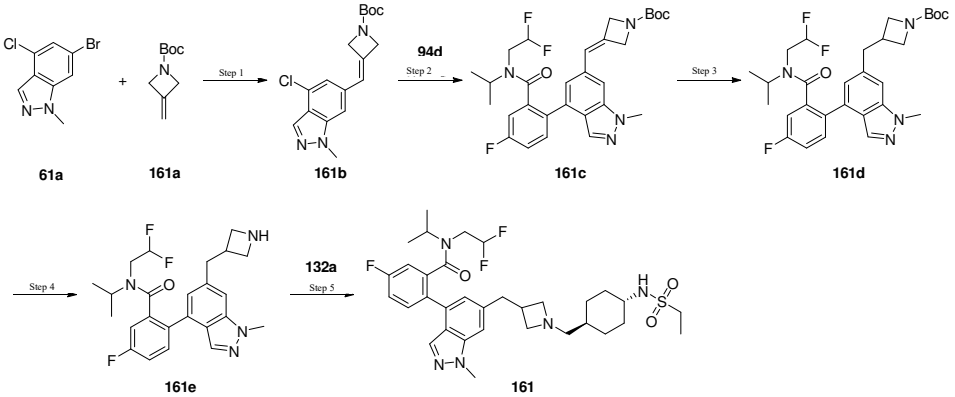
Compound **159b** (50 mg, 22.41 μmol), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a** (32.21 mg, 146.89 μmol) and triethylamine (37.16 mg, 367.23 μmol) were dissolved in methanol (1.5 mL), and stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (23.85 mg, 379.47 μmol) was added, and the mixture was stirred at room temperature for 2.0 hours. A saturated aqueous sodium bicarbonate solution (5 mL) was added to the reaction mixture, which was then extracted with dichloromethane (5 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 24%-54%), to obtain the title Compound **159** (9.45 mg, 15.45 μmol, yield: 12.62 %) as white solid.

MS m/z (ESI): 612.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 – 7.74 (m, 1H), 7.71 – 7.54 (m, 2H), 7.50 – 7.25 (m, 2H), 7.17 – 6.93 (m, 2H), 4.34 – 4.02 (m, 4H), 3.87 – 3.35 (m, 6H), 3.19 – 3.04 (m, 3H), 3.01 – 2.91 (m, 3H), 2.89 – 2.72 (m, 1H), 2.46 – 2.17 (m, 3H), 1.91 – 1.70 (m, 4H), 1.25 – 1.11 (m, 7H), 1.03 – 0.86 (m, 3H), 0.18 (s, 1H).

Example 161

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}azacyclobutan-3-yl)methyl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **161**



Step 1

3-[(4-chloro-1-methyl-1*H*-indazol-6-yl)methylene]azacyclobutan-1-tert-butyl formate **161b**

Compound **61a** (500 mg, 2.04 mmol), 3-methyleneazacyclobutan-1-tert-butyl formate **161a** (448.03 mg, 2.65 mmol) and tetrabutylammonium acetate (1.23 g, 4.07 mmol) were dissolved in dioxane (9.0 mL). Palladium acetate (91.45 mg, 407.33 μmol) and Xphos (149.02 mg, 203.66 μmol) were added, and the mixture was stirred at 80°C under a

nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **161b** (465 mg, 1.39 mmol, yield: 68.40%) as yellow oil.
MS m/z (ESI): 334.1 [M+1]

Step 2

3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methylene]azacyclobutan-1-tert-butyl formate **161c**

Compound **161b** (250 mg, 748.92 μmol) and Compound **94d** (333.60 mg, 898.71 μmol) were dissolved in dioxane (6.0 mL) and water (1.0 mL). Potassium phosphate (476.91 mg, 2.25 mmol) and $Pd(dtbpf)Cl_2$ (48.81 mg, 74.89 μmol) were added, and the mixture was stirred at 95°C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **161c** (290 mg, 534.47 μmol, yield: 71.37%) as yellow solid.
MS m/z (ESI): 543.2 [M+1]

Step 3

3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-tert-butyl formate **161d**

Compound **161c** (290 mg, 534.47 μmol) was dissolved in tetrahydrofuran (10 mL), followed by the addition of 10% Pd/C (304.87 mg, 286.48 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at 25°C for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **161d** (240 mg, 440.68 μmol, yield: 82.45%).
MS m/z (ESI): 545.2 [M+1]

Step 4

2-{6-[(azacyclobutan-3-yl)methyl]-1-methyl-1*H*-indazol-4-yl}-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **161e**

Compound **161d** (120 mg, 220.34 μmol) was dissolved in methane dioxide (2.5 mL), followed by the addition of trifluoroacetic acid (25.12 mg, 220.34 μmol, 16.98 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **161e** (95 mg, 213.73 μmol). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 445.2 [M+1]

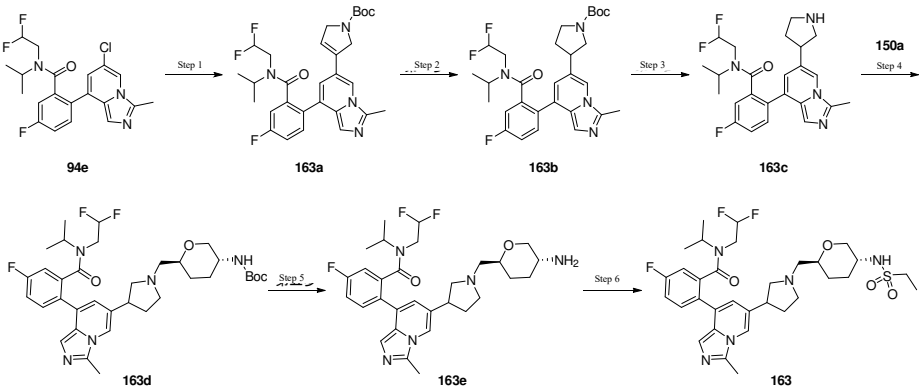
Step 5

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}azacyclobutan-3-yl)methyl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **161**

The crude product of Compound **165e** (123.06 mg, 220.34 μmol, trifluoroacetate) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (66.89 mg, 661.02 μmol) and Compound **132a**(57.98 mg, 264.41 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (41.96 mg, 667.63 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 37%-67%), to obtain the title Compound **161** (21.95 mg, 33.88 μmol, yield: 15.38%) as white solid.
MS m/z (ESI):648.4 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 – 7.74 (m, 1H), 7.64 – 7.55 (m, 1H), 7.47 – 7.34 (m, 3H), 6.97 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 5.93 – 5.56 (m, 1H), 4.07 – 3.97 (m, 3H), 3.62 – 3.38 (m, 2H), 3.29 – 3.21 (m, 3H), 2.99 – 2.90 (m, 5H), 2.82 – 2.74 (m, 2H), 2.70 – 2.61 (m, 1H), 2.20 – 2.12 (m, 2H), 1.87 – 1.77 (m, 2H), 1.74 – 1.66 (m, 2H), 1.23 – 1.09 (m, 6H), 0.94 – 0.81 (m, 5H), 0.14 – 0.03 (m, 3H).

Example 163

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-5-fluoro-*N*-(isopropyl)benzamide **163**



Step 1

3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **163a**

Compound **94e** (500 mg, 1.22 mmol) was dissolved in dioxane (8.0 mL) and water (2.0 mL). Potassium phosphate (766.9 mg, 3.66 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (540.19 mg, 1.83 mmol) and Pd(dtbpf)Cl_2 (79.51 mg, 122.0 μmol) were added, and the mixture was stirred at 95°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **163a** (400 mg, 737.2 μmol, yield: 60.43%) as brown solid.

MS m/z (ESI): 543.4 [M+1]

Step 2

3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **163b**

Compound **163a** (400 mg, 737.2 μmol) was dissolved in tetrahydrofuran (10 mL), followed by the addition of 10% Pd/C (100 mg, 939.67 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **163b** (100 mg, 183.62 μmol, yield: 29.4%).

MS m/z (ESI): 545.4 [M+1]

Step 3

N-(2,2-difluoroethyl)-5-fluoro-2-[3-methyl-6-(pyrrolidin-3-yl)imidazo[1,5-*a*]pyridin-8-yl]-*N*-(isopropyl)benzamide **163c**

Compound **163b** (100 mg, 183.62 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **163c** (102 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 445.4 [M+1]

Step 4

N-[(3*R*,6*S*)-6-{[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)pyrrolidin-1-yl]methyl}oxacyclohexan-3-yl]tert-butyl carbamate **163d**

The crude product of Compound **163c** (102 mg) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (37.04 mg, 366.00 μmol) and Compound **150a**(50 mg, 218.08 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (34.50 mg, 549.00 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for 2.0 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using ethyl acetate/ethanol as an elution system, to obtain the title Compound **163d** (100 mg, 152.03 μmol, yield: 83.08 %) as yellow solid.

MS m/z (ESI):658.4 [M+1]

Step 5

2-[6-(1-{[(2*S*,5*R*)-5-aminooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-

(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **163e**

Compound **163d** (100 mg, 152.03 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **163e** (100 mg, 179.32 μmol, yield: 117.95%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 558.2 [M+1]

Step 6

N-(2,2-difluoroethyl)-2-[6-(1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-5-fluoro-*N*-(isopropyl)benzamide **163**

The crude product of Compound **163e** (90 mg, 133.99 μmol, trifluoroacetate) was dissolved in dichloromethane (3.0 mL), followed by the addition of ethanesulfonyl chloride (34.46 mg, 267.99 μmol) and triethylamine (67.79 mg, 669.97 μmol), and the mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 32%-62%), to obtain the title Compound **163** (41.27 mg, 63.52 μmol, yield: 47.4%) as white solid.

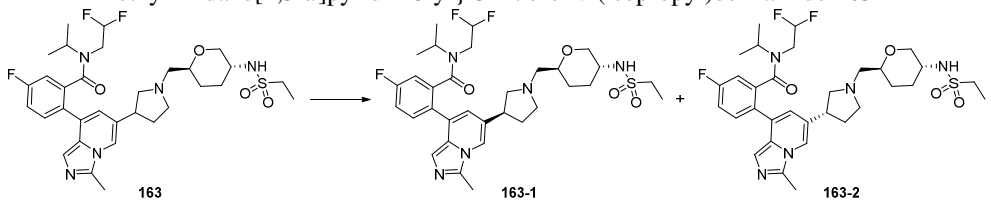
MS m/z (ESI):650.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.73 – 7.64 (m, 1H), 7.42 – 7.33 (m, 1H), 7.31 – 7.22 (m, 1H), 7.10 (s, 1H), 6.77 (s, 1H), 6.01 – 5.57 (m, 1H), 4.07 – 3.94 (m, 1H), 3.74 – 3.57 (m, 2H), 3.51 – 3.35 (m, 2H), 3.29 – 3.00 (m, 6H), 2.98 – 2.87 (m, 1H), 2.86 – 2.71 (m, 1H), 2.68 – 2.54 (m, 6H), 2.37 – 2.22 (m, 1H), 2.16 – 2.04 (m, 1H), 1.97 – 1.70 (m, 2H), 1.59 – 1.37 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 0.99 – 0.88 (m, 3H), 0.47 – 0.26 (m, 3H).

Examples 163-1 and 163-2

N-(2,2-difluoroethyl)-2-{6-[(3*S*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]- 3-methylimidazo[1,5-*a*]pyridin-8-yl}-5-fluoro-*N*-(isopropyl)benzamide **163-1**

N-(2,2-difluoroethyl)-2-{6-[(3*R*)-1-{[(2*S*,5*R*)-5-ethanesulfonamidooxacyclohexan-2-yl]methyl}pyrrolidin-3-yl]- 3-methylimidazo[1,5-*a*]pyridin-8-yl}-5-fluoro-*N*-(isopropyl)benzamide **163-2**



Compound **163** (40 mg, 61.56 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 10 um), mobile phase: carbon dioxide/[acetonitrile/isopropanol (0.1% ammonia water)], elution gradient: 55%), to obtain the title Compounds **163-1** (5.62 mg, 8.65 μmol, yield: 14.05%) and **163-2** (5.6 mg, 8.62 μmol, yield: 14.0%).

Single-configuration Compound 163-1:

MS m/z (ESI):649.5 [M+1]

SFC analysis: retention time: 1.708 min; chromatographic column: Chiralpak IC-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/[IPA+ACN (0.05% DEA)]: elution gradient: 40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 7.73 – 7.66 (m, 1H), 7.41 – 7.34 (m, 1H), 7.27 (dd, J = 2.4, 8.4 Hz, 1H), 7.10 (s, 1H), 6.76 (s, 1H), 6.02 – 5.61 (m, 1H), 4.07 – 3.97 (m, 1H), 3.72 – 3.58 (m, 2H), 3.52 – 3.37 (m, 2H), 3.28 – 2.99 (m, 6H), 2.98 – 2.89 (m, 1H), 2.84 – 2.71 (m, 1H), 2.68 – 2.55 (m, 6H), 2.37 – 2.25 (m, 1H), 2.16 – 2.06 (m, 1H), 1.96 – 1.85 (m, 1H), 1.80 – 1.72 (m, 1H), 1.54 – 1.46 (m, 1H), 1.33 – 1.30 (m, 4H), 0.95 (d, J = 6.4 Hz, 3H), 0.36 (t, J = 6.8 Hz, 3H).

Single-configuration Compound 163-2:

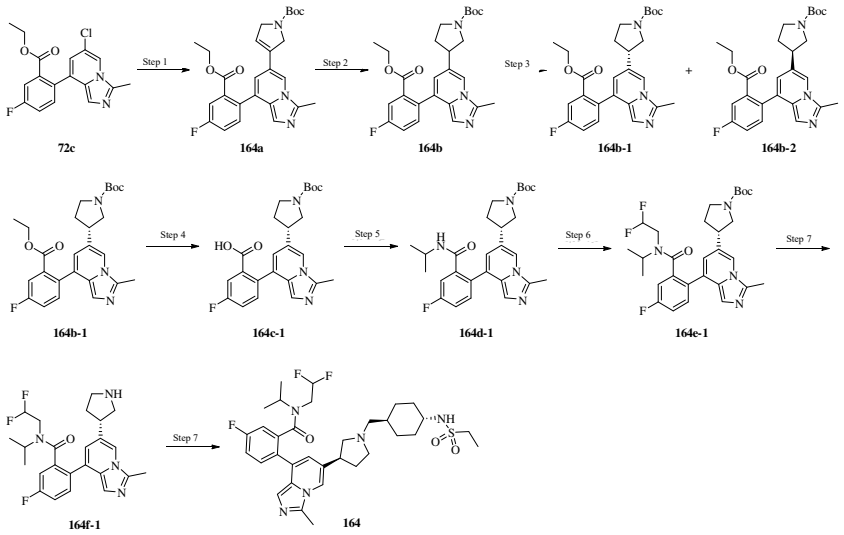
MS m/z (ESI):649.5 [M+1]

SFC analysis: retention time: 1.08 min; chromatographic column: Chiralpak IC-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/[IPA+ACN (0.05% DEA)]: elution gradient: 40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.72 – 7.65 (m, 1H), 7.41 – 7.33 (m, 1H), 7.31 – 7.25 (m, 1H), 7.10 (s, 1H), 6.79 – 6.71 (m, 1H), 5.99 – 5.56 (m, 1H), 4.08 – 3.95 (m, 1H), 3.73 – 3.58 (m, 2H), 3.53 – 3.35 (m, 2H), 3.29 – 3.00 (m, 6H), 2.97 – 2.87 (m, 1H), 2.85 – 2.72 (m, 1H), 2.67 – 2.57 (m, 6H), 2.38 – 2.24 (m, 1H), 2.16 – 2.05 (m, 1H), 1.97 – 1.71 (m, 2H), 1.55 – 1.45 (m, 1H), 1.34 – 1.28 (m, 4H), 0.95 (d, J = 6.8 Hz, 3H), 0.48 – 0.26 (m, 3H).

Example 164

N-(2,2-difluoroethyl)-5-fluoro-2-{3-methyl-6-[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **164**



Step 1

3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-yl}-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate **164a**

Compound **72c** (2.35 g, 7.06 mmol) was dissolved in dioxane (25 mL) and water (5.0 mL). Potassium phosphate (4.50 g, 21.19 mmol), 3-(tetramethyl-1,3,2-dioxaboran-2-yl)-2,5-dihydro-1*H*-pyrrol-1-tert-butyl formate (3.13 g, 10.59 mmol) and Pd(dtbpf)Cl_2 (460.28 mg, 706.22 μmol) were added, and the mixture was stirred at 95°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **164a** (2.7 g, 5.80 mmol, yield: 82.13%) as brown solid.

MS m/z (ESI): 466.3 [M+1]

Step 2

3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-yl}-pyrrolidin-1-tert-butyl formate **164b**

Compound **164a** (2.7 g, 5.80 mmol) was dissolved in tetrahydrofuran (30.0 mL), followed by the addition of 10% Pd/C (500 mg, 469.84 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at 40℃ to allow for reacting for 8.0 hour. The reaction mixture was filtered, the filtrate was concentrated under a reduced pressure, and the residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 38%-58%), to obtain the title Compound **164b** (1.0 g, 2.14 mmol, yield: 36.88%).

MS m/z (ESI): 468.2 [M+1]

Step 3

(3*S*)-3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-yl}-pyrrolidin-1-tert-butyl formate **164b-1**

(3*R*)-3-{8-[2-(ethoxycarbonyl)-4-fluorophenyl]-3-methylimidazo[1,5-a]pyridin-6-yl}-pyrrolidin-1-tert-butyl formate **164b-1**

Compound **164b** (1.0 g, 2.14 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um), mobile phase: 5%-25% (v/v) carbon dioxide-ethanol (0.05% diethylamide)), to obtain the title Compounds **164b-1** (325 mg, 695.14 μmol, yield: 32.5%) and **164b-2** (233 mg, 498.36 μmol, yield: 23.0%).

Single-configuration Compound 164b-1:

MS m/z (ESI):468.2 [M+1]

SFC analysis: retention time: 1.409 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/EtOH (0.05% DEA): elution gradient: 5%-25%.

Single-configuration Compound 164b-2:

MS m/z (ESI):468.2 [M+1]

SFC analysis: retention time: 1.547 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/EtOH (0.05% DEA): elution gradient: 5%-25%.

Step 4

2-{6-[(3*S*)-1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl]-3-methylimidazo[1,5-a]pyridin-8-yl}-5-fluorobenzoic acid

164c-1

Compound **164b-1**(325 mg, 695.14 μmol) was dissolved in ethanol (1.0 mL), tetrahydrofuran (1.0 mL) and water (1.0 mL), followed by the addition of $LiOH.H_2O$ (87.50 mg, 2.09 mmol), and the mixture was stirred at 25°C to allow for reacting for 12 hours. The reaction mixture was regulated to PH = 3 with 1M HCl, and extracted with trichloromethane/isopropanol (5/1; 20 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **164c-1** (300 mg, 682.63 μmol, yield: 98.2%) was obtained as brown solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 440.4 [M+1]

Step 5

(3*S*)-3-(8-{4-fluoro-2-[(isopropyl)aminoformyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **164d-1**

Compound **164c-1** (250 mg, 568.86 μmol) was dissolved in dichloromethane (4.0 mL), followed by the addition of prop-2-amine (40.35 mg, 682.63 μmol) and triethylamine (172.69 mg, 1.71 mmol). In an ice bath, HATU (259.56 mg, 682.63 μmol) was slowly added, and the mixture was stirred at room temperature for 2.0 hours. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **164d-1** (190 mg, 395.36 μmol, yield: 69.50%) as yellow solid.

MS m/z (ESI): 481.4 [M+1]

Step 6

(3*S*)-3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)pyrrolidin-1-tert-butyl formate **164e-1**

Compound **164d-1** (170 mg, 353.74 μmol) was dissolved in DMF(0.5 mL), followed by the addition of sodium hydride (30 mg, 750.07 μmol, 60%purity). The reaction mixture was stirred at 0°C for 0.5 hours, followed by the addition of 2,2-difluoroethyltrifluoromethanesulfonate (98.46 mg, 459.87 μmol), and the mixture was stirred at room temperature to allow for reacting for 12 hours. A saturated aqueous ammonium chloride solution (15 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **164e-1** (35 mg, 64.27 μmol, yield: 18.17%) as yellow solid.

MS m/z (ESI): 545.5 [M+1]

Step 7

N-(2,2-difluoroethyl)-5-fluoro-2-{3-methyl-6-[(3*S*)-pyrrolidin-3-yl]imidazo[1,5-a]pyridin-8-yl}-*N*-(isopropyl)benzamide **164f-1**

Compound **164e-1** (40 mg, 73.45 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **164f-1** (40.77 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 445.2 [M+1]

Step 8

N-(2,2-difluoroethyl)-5-fluoro-2-{3-methyl-6-[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **164**

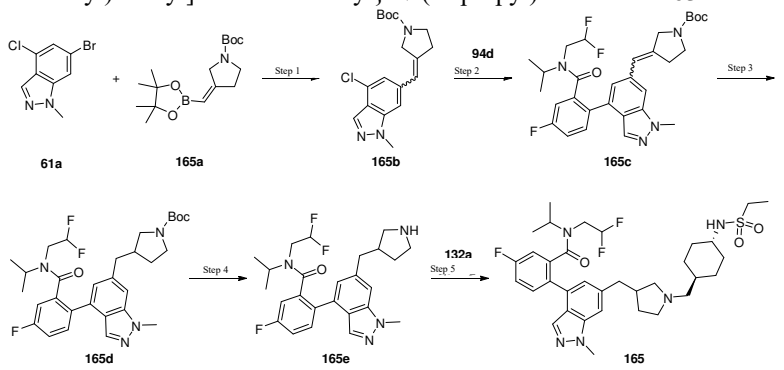
The crude product of Compound **164f-1** (40.77 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(20 mg, 91.20 μmol) and triethylamine (14.77 mg, 146.00 μmol) was dissolved in methanol (1.0 mL), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (13.76 mg, 219.00 μmol) was added, and the mixture was stirred at room temperature for 2.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **164** (6.46 mg, 9.97 μmol, yield: 13.66 %) as white solid.

MS m/z (ESI): 648.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 0.12H), 7.94 (s, 1H), 7.71 – 7.61 (m, 1H), 7.48 – 7.35 (m, 2H), 6.99 (s, 2H), 6.63 (m, 1H), 5.91 – 5.52 (m, 1H), 3.69 – 3.43 (m, 3H), 3.17 – 2.90 (m, 4H), 2.84 – 2.55 (m, 6H), 2.36 – 2.13 (m, 3H), 1.91 – 1.75 (m, 5H), 1.53 – 1.43 (m, 1H), 1.34 (m, 1H), 1.18 (m, 4H), 0.93 – 0.80 (m, 6H), 0.32 (m, 3H).

Example 165

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)methyl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **165**



Step 1

3-[(4-chloro-1-methyl-1*H*-indazol-6-yl)methylene]pyrrolidin-1-tert-butyl formate **165b**

Compound **61a** (500 mg, 2.04 mmol) was dissolved in dioxane (6.0 mL) and water (1.0 mL). Sodium carbonate (647.59 mg, 6.11 mmol), 3-[(tetramethyl-1,3,2-dioxaboran-2-yl)methylene]-pyrrolidin-1-tert-butyl formate (692.72 mg, 2.24 mmol) and Pd(dppf)Cl_2 (149.02 mg, 203.66 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (100 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **165b** (700 mg, 2.01 mmol, yield: 98.81%) as yellow solid.

MS m/z (ESI): 348.1 [M+1]

Step 2

3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methylene]pyrrolidin-1-tert-butyl formate **165c**

Compound **165b** (300 mg, 862.47 μmol) and Compound **94d** (384.18 mg, 1.03 mmol) were dissolved in dioxane (8.0 mL) and water (1.0 mL). Potassium phosphate (507.49 mg, 2.39 mmol) and Pd(dtbpf)Cl_2 (56.21 mg, 86.25 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **165c** (400 mg, 718.63 μmol, yield: 83.32%) as yellow oil.

MS m/z (ESI): 557.5 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.47 (td, J = 5.6, 8.6 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.94 – 6.84 (m, 1H), 6.50 – 6.34 (m, 1H), 5.86 – 5.44 (m, 1H), 3.98 (d, J = 5.4 Hz, 3H), 3.60 – 3.45 (m, 2H), 3.40 (dt, J = 6.4, 12.8 Hz, 2H), 2.96 – 2.75 (m, 2H), 2.70 (br t, J = 7.0 Hz, 1H), 1.13 (s, 12H), 0.76 (d, J = 6.4 Hz, 3H), -0.01 (d, J = 6.4 Hz, 3H).

Step 3

3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methyl]pyrrolidin-1-tert-butyl formate **165d**

Compound **165c** (300 mg, 538.97 μmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (196.38 mg, 1.62 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at 50°C for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **165d** (300 mg, 537.02 μmol, yield: 99.6%).

MS m/z (ESI): 559.4 [M+1]

Step 4

N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(pyrrolidin-3-yl)methyl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **165e**

Compound **165d** (60 mg, 107.40 μmol) was dissolved in methane dioxide (5.0 mL), followed by the addition of trifluoroacetic acid (12.25 mg, 107.40 μmol, 8.27 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **165e** (49.25 mg). The crude product was directly used in the next step of reaction without

purification.
MS m/z (ESI): 459.3 [M+1]

Step 5

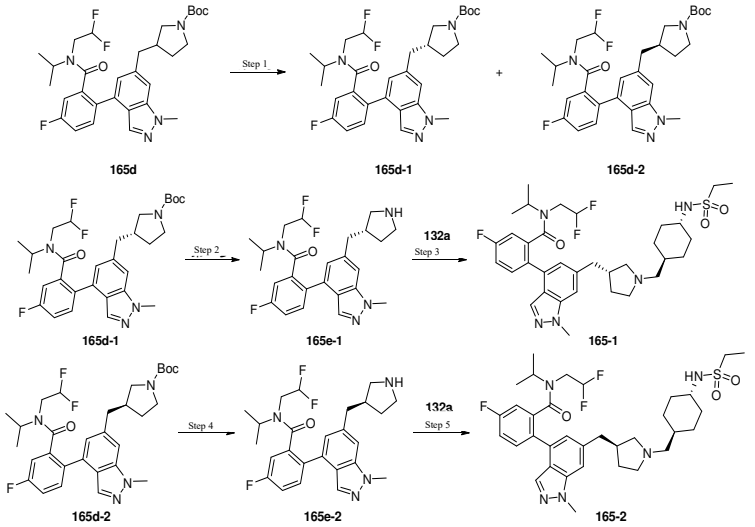
N-(2,2-difluoroethyl)-5-fluoro-2-{1-methyl-6-[(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl)methyl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **165**

The crude product of Compound **165e** (49.25 mg) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (32.61 mg, 322.23 μmol) and Compound **132a**(25.91 mg, 118.15 μmol), and the mixture was stirred at room temperature for 1.0 hours. Sodium cyanoborohydride (13.50 mg, 214.82 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for 12 hours. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **165** (18.7 mg, 28.26 μmol, yield: 26.3%)
MS m/z (ESI):662.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.66 – 7.60 (m, 1H), 7.42 (s, 1H), 7.37 (dt, J = 2.8, 8.4 Hz, 1H), 7.26 (dd, J = 2.8, 8.8 Hz, 1H), 7.02 (s, 1H), 5.92 – 5.56 (m, 1H), 4.07 (s, 3H), 3.67 – 3.52 (m, 2H), 3.05 – 2.99 (m, 2H), 2.86 (d, J = 7.6 Hz, 2H), 2.78 – 2.69 (m, 2H), 2.62 – 2.51 (m, 2H), 2.36 – 2.24 (m, 3H), 2.07 – 1.94 (m, 4H), 1.90 – 1.81 (m, 2H), 1.66 – 1.53 (m, 2H), 1.30 (br t, J = 7.2 Hz, 6H), 1.06 – 0.97 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H), 0.16 (d, J = 6.8 Hz, 3H).

Examples 165-1 and 165-2

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165-1**

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*R*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165-2**



Step 1

(3*S*)-3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methyl]pyrrolidin-1-tert-butyl formate **165d-1**

(3*R*)-3-[(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)methyl]pyrrolidin-1-tert-butyl formate **165d-2**

Compound **165d** (270 mg, 483.32 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALPAK IF (250 mm * 30 mm, 10 um), mobile phase: n-hexane-isopropanol/acetonitrile (0.1%isopropylamine); elution gradient: 15%-15%), to obtain the title Compounds **165d-1** (82 mg, 146.79 μmol, yield: 30.37%) and **165d-2** (90 mg, 161.11 μmol, yield: 33.33%).

Single-configuration Compound 165d-1:

MS m/z (ESI):559.5 [M+1]
Chiral HPLC analysis: retention time: 3.719 min; chromatographic column: Chiralpak IF-3 50 x 4.6mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-isopropanol/acetonitrile (0.05% isopropylamine): elution gradient: 10%-10%.

Single-configuration Compound 165d-2:

MS m/z (ESI):559.4 [M+1]
Chiral HPLC analysis: retention time: 3.333 min; chromatographic column: Chiralpak IF-3 50 x 4.6mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-isopropanol/acetonitrile (0.05% isopropylamine): elution gradient: 10%-10%.

Steps 2 and 4

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*S*)-pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165e-1**

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*R*)-pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165e-2**

Compound **165d-1/165d-2** (82 mg/90 mg, 146.79 μmol/161.11 μmol) was dissolved in methane dioxide (5.0 mL/5.0 mL), followed by the addition of trifluoroacetic acid (1.0 mL/1.0 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **165e-1/165e-2** (67.3 mg/73.87 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 165e-1:
MS m/z (ESI): 459.3 [M+1]
Single-configuration Compound 165e-2:
MS m/z (ESI): 459.4 [M+1]

Steps 3 and 5

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*S*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165-1**

N-(2,2-difluoroethyl)-5-fluoro-2-(1-methyl-6-{[(3*R*)-1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}pyrrolidin-3-yl]methyl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **165-2**

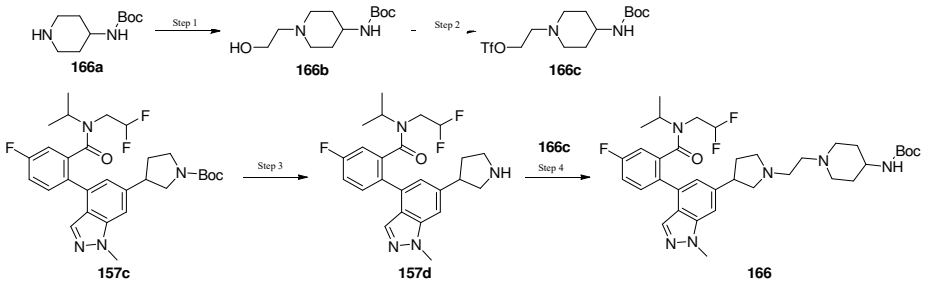
The crude product of Compound **165e-1/165e-2** (67.3 mg/73.87 mg) was dissolved in methanol (2.0 mL /2.0 mL), followed by the addition of triethylamine (35.68 mg/48.91 mg, 352.64 μmol/483.32 μmol) and Compound **132a**(28.36 mg/38.86 mg, 129.3 μmol/177.22 μmol), and the mixture was stirred at room temperature for (1.0/1.0) hour. Sodium cyanoborohydride (14.77 mg / 20.25 mg, 235.09 μmol/322.21 μmol) was added, and the mixture was stirred at room temperature to allow for reacting for (12/12) hours. An aqueous ammonium chloride solution (20 mL/20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3/10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 19%-49%/40%-70%), to obtain the title Compound **165-1/165-2** (12.02 mg/32.24 mg, 48.71 μmol/60.81 μmol, yield: 15.45 %/30.24 %)

Single-configuration Compound 165-1:
MS m/z (ESI):662.4 [M+1]
Chiral SFC: retention time: 1.436 min; chromatographic column: Chiralcel OD-3 50 X 4.6 mm I.D., 3 um; mobile phase: CO2/MeOH (0.05%DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (s, 1H), 7.51 – 7.44 (m, 1H), 7.27 (s, 1H), 7.22 (dt, J = 2.6, 8.8 Hz, 1H), 7.12 (dd, J = 2.6, 8.8 Hz, 1H), 6.88 (s, 1H), 5.81 – 5.38 (m, 1H), 3.92 (s, 3H), 3.52 – 3.38 (m, 2H), 3.13 – 3.02 (m, 1H), 3.00 – 2.92 (m, 1H), 2.87 (q, J = 7.2 Hz, 2H), 2.72 (d, J = 8.0 Hz, 2H), 2.68 – 2.55 (m, 2H), 2.52 – 2.41 (m, 2H), 2.26 – 2.11 (m, 3H), 1.89 – 1.79 (m, 3H), 1.77 – 1.67 (m, 2H), 1.55 – 1.39 (m, 2H), 1.15 (t, J = 7.2 Hz, 5H), 0.86 (d, J = 12.0 Hz, 2H), 0.76 (d, J = 6.4 Hz, 3H), 0.01 (d, J = 6.4 Hz, 3H).

Single-configuration Compound 165-2:
MS m/z (ESI):662.5 [M+1]
Chiral SFC: retention time: 1.476 min; chromatographic column: Chiralcel OD-3 50 X 4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.68 – 7.59 (m, 1H), 7.45 – 7.33 (m, 2H), 7.26 (dd, J = 2.6, 8.8 Hz, 1H), 7.02 (s, 1H), 5.92 – 5.54 (m, 1H), 4.07 (s, 3H), 3.65 – 3.51 (m, 2H), 3.27 – 3.17 (m, 1H), 3.15 – 3.07 (m, 1H), 3.02 (q, J = 7.4 Hz, 2H), 2.87 (d, J = 7.2 Hz, 2H), 2.81 – 2.67 (m, 2H), 2.64 – 2.52 (m, 2H), 2.40 – 2.22 (m, 3H), 2.05 – 1.93 (m, 3H), 1.92 – 1.81 (m, 2H), 1.68 – 1.53 (m, 2H), 1.30 (br t, J = 7.3 Hz, 5H), 1.08 – 0.96 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H), 0.16 (d, J = 6.4 Hz, 3H).

Example 166

N-(1-{2-[3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]ethyl}piperidin-4-yl)tert-butyl carbamate **166**



Step 1

N-[1-(2-hydroxylethyl) piperidin-4-yl]tert-butyl carbamate **166b**

N-(piperidin-4-yl)tert-butyl carbamate **166a** (10 g, 49.93 mmol) was dissolved in acetonitrile (50 mL). Potassium carbonate (6.90 g, 49.93 mmol) and 2-bromoethanol (6.24 g, 49.93 mmol) were added, and the mixture was stirred at room temperature to allow for reacting for 12 hours. Water (150 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **166b** (8 g, 32.74 mmol, yield: 65.58%).

MS m/z (ESI): 245.2 [M+1]

Step 2

N-{1-[2-(trifluoromethylsulfonyloxy)ethyl]piperidin-4-yl}tert-butyl carbamate **166c**

Compound **166b** (100 mg, 409.28 μmol) and triethylamine (62.12 mg, 613.92 μmol) were dissolved in dichloromethane (3.0 mL). The mixture was cooled to -78°C, followed by the slow dropwise addition of the dichloromethane solution (3.0 mL) of trifluoromethanesulfonic anhydride (150.12 mg, 532.07 μmol). The reaction mixture was slowly warmed to 0°C, and stirred to allow for reacting for 2.0 hours. The reaction mixture was directly used in the next step of reaction without further treatment.

Step 3

N-(2,2-difluoroethyl)-5-fluoro-2-[1-methyl-6-(pyrrolidin-3-yl)-1*H*-indazol-5-yl]-*N*-(isopropyl)benzamide **157d**

Compound **157c** (50.00 mg, 91.81 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (999.97 mg, 8.77 mmol, 675.66 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a saturated aqueous sodium bicarbonate solution (20 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **157d** (40.81 mg, 91.81 μmol, yield: 100%) was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 445.1 [M+1]

Step 4

N-(1-{2-[3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]ethyl}piperidin-4-yl)tert-butyl carbamate **166**

The crude product of Compound **157d** (40 mg, 89.99 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (9.11 mg, 89.99 μmol). The reaction mixture was cooled to 0°C, followed by the addition of the dichloromethane solution (4.0 mL) of Compound **166c** (101.61 mg, 269.97 μmol), and the mixture was stirred at room temperature for 12 hours . Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 52%-82%), to obtain the title Compound **166** (14.16 mg, 21.11 μmol, yield: 23.46%)

MS m/z (ESI):671.4 [M+1]

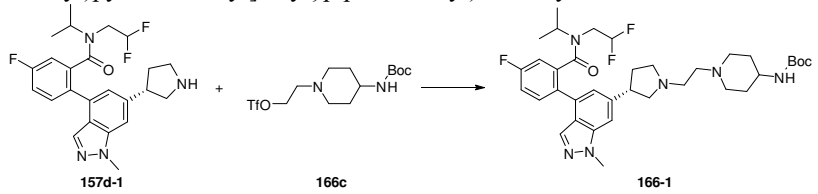
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 1H), 7.58 – 7.52 (m, 1H), 7.29 (s, 1H), 7.25 – 7.21 (m, 1H), 7.16 (dd, J = 2.4, 8.4 Hz, 1H), 7.07 (s, 1H), 6.04 – 5.69 (m, 1H), 4.49 – 4.37 (m, 1H), 4.08 (s, 3H), 3.64 – 3.54 (m, 3H), 3.53 – 3.46 (m, 2H), 3.14 – 3.01 (m, 2H), 2.90 – 2.86 (m, 2H), 2.79 – 2.69 (m, 2H), 2.67 – 2.61 (m, 1H), 2.59 – 2.52 (m, 2H), 2.44 – 2.31 (m, 1H), 2.24 – 2.12 (m, 2H), 2.05 – 1.99 (m, 1H), 1.95 – 1.91 (m, 2H), 1.45 (s, 9H), 1.39 – 1.34 (m, 2H), 1.28 – 1.26 (m, 2H), 0.90 – 0.87 (m, 3H), 0.12 (d, J = 6.4 Hz, 2H)

Examples 166-1 and 166-2

N-(1-{2-[(3*S*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)pyrrolidin-1-yl]ethyl}piperidin-4-yl)tert-butyl carbamate **166-1**

N-(1-{2-[(3*R*)-3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-

yl)pyrrolidin-1-yl]ethyl}piperidin-4-yl)tert-butyl carbamate **166-2**



The crude product of Compound **157d-1/157d-2** (40.81 mg/40.81 mg, 91.81 μmol/91.81 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (18.58 mg/18.58 mg, 183.63 μmol/183.63 μmol). The reaction mixture was cooled to 0°C, followed by the addition of the dichloromethane solution (2.0 mL/2.0 mL) of Compound **166c**(34.56 mg/34.56 mg, 91.81 μmol/91.81 μmol), and the mixture was stirred at room temperature for 12 hours . Water (50 mL/50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3/50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 53%-83%/53%-83%), to obtain the title Compound **166-1/166-2** (1.23 mg/7.31 mg, 1.83 μmol/10.9 μmol, yield: 2.00%/11.87%).

Single-configuration Compound 166-1:

MS m/z (ESI):671.3 [M+1]

Chiral SFC: retention time: 1.177 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.59 – 7.52 (m, 1H), 7.37 – 7.30 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.14 (m, 1H), 7.07 (s, 1H), 6.06 – 5.68 (m, 1H), 4.61 – 4.37 (m, 1H), 4.09 (s, 3H), 3.65 – 3.46 (m, 4H), 3.26 – 2.99 (m, 3H), 2.98 – 2.88 (m, 3H), 2.87 – 2.67 (m, 4H), 2.67 – 2.56 (m, 2H), 2.49 – 2.30 (m, 2H), 2.25 – 2.13 (m, 2H), 2.04 – 1.88 (m, 4H), 1.45 (s, 9H), 0.88 (d, J = 6.4 Hz, 3H), 0.12 – 0.09 (m, 2H).

Single-configuration Compound 166-2:

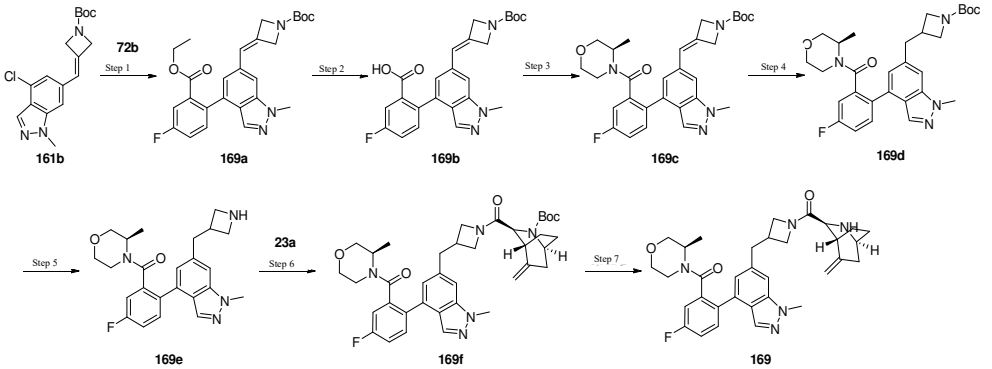
MS m/z (ESI):671.5 [M+1]

Chiral SFC: retention time: 1.172 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.59 – 7.52 (m, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.21 (m, 1H), 7.19 – 7.14 (m, 1H), 7.07 (s, 1H), 6.05 – 5.69 (m, 1H), 4.53 – 4.39 (m, 1H), 4.09 (s, 3H), 3.63 – 3.45 (m, 4H), 3.20 – 3.00 (m, 3H), 2.94 – 2.86 (m, 3H), 2.82 – 2.73 (m, 2H), 2.71 – 2.62 (m, 2H), 2.61 – 2.53 (m, 2H), 2.46 – 2.32 (m, 2H), 2.21 – 2.12 (m, 2H), 2.01 – 1.88 (m, 4H), 1.45 (s, 9H), 0.91 – 0.86 (m, 3H), 0.13 – 0.09 (m, 2H).

Example 169

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-6-({1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}methyl)-1*H*-indazole **169**



Step 1

3-({4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1H-indazol-6-yl}methylene)azacyclobutan-1-tert-butyl

formate **169a**

Compound **161b** (665 mg, 1.99 mmol) and Compound **72b** (878.91 mg, 2.39 mmol) were dissolved in dioxane (9.0 mL) and water (1.5 mL). Potassium phosphate (1.27 g, 5.98 mmol) and Pd(dtbpf)Cl_2 (129.84 mg, 199.21 μmol) were added, and the mixture was stirred at 95°C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **169a** (487 mg, 1.05 mmol, yield: 52.51%) as yellow oil.

MS m/z (ESI): 466.2 [M+1]

Step 2

2-[6-({1-[(tert-butoxy)carbonyl]azacyclobutan-3-ylidene}methyl)-1-methyl-1*H*-indazol-4-yl]-5-fluorobenzoic acid **169b**

Compound **169a** (487 mg, 1.05 mmol) was dissolved in ethanol (5 mL) and water (2.5 mL), followed by the addition of LiOH.H_2O (439.00 mg, 10.46 mmol), and the mixture was stirred at 50°C to allow for reacting for 12 hours. The mixture was cooled to room temperature, followed by removing the organic solvent under a reduced pressure. The mixture was regulated to PH < 7 by adding 1M HCl, and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **169b** (450 mg, 1.03 mmol, yield: 98.33%) was obtained as yellow oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 438.1 [M+1]

Step 3

3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methylene]azacyclobutan-1-tert-butyl formate **169c**

Compound **169b** (200 mg, 457.18 μmol), triethylamine (138.79 mg, 1.37 mmol) and HATU (208.60 mg, 548.62 μmol) were dissolved in dichloromethane (3.0 mL), and stirred at room temperature for 10 min, followed by the addition of (3*R*)-3-methylmorpholine (50.87 mg, 502.90 μmol). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **169c** (195 mg, 374.57 μmol, yield: 81.93%).

MS m/z (ESI): 521.2 [M+1]

Step 4

3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-tert-butyl formate **169d**

Compound **169c** (195 mg, 374.57 μmol) was dissolved in tetrahydrofuran (3.0 mL), followed by the addition of 10% Pd/C (224.14 mg, 2.11 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at 25°C for 3.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **169d** (180 mg, 344.43 μmol, yield: 91.95%).

MS m/z (ESI): 523.2 [M+1]

Step 5

6-[(azacyclobutan-3-yl)methyl]-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **169e**

Compound **169d** (90 mg, 172.21 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **169e** (70 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 423.1 [M+1]

Step 6

(1*S*,3*S*,4*R*)-3-{3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-carbonyl}-5-methylene-2-azabicyclo[2.2.2]octan-2-tert-butyl carboxylate **169f**

Compound **23a**(38.37 mg, 143.52 μmol) and *N,N*-diisopropylethylamine (118.04 mg, 913.30 μmol) were dissolved in DCM (3.0 mL). The mixture was cooled to 0°C, followed by the addition of EDCI (37.77 mg, 197.01 μmol), HOBT (26.97 mg, 199.62 μmol) and the crude product of Compound **169e** (70 mg), and the mixture was then stirred at room temperature for 12 hours. The reaction mixture was diluted with a saturated aqueous sodium bicarbonate solution (10 mL), and extracted with dichloromethane (15 mL x 3), and the organic phase was dried over anhydrous

sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **169e** (70 mg, 104.20 μmol, yield: 79.86%) as colorless oil.
MS m/z (ESI): 672.6 [M+1]

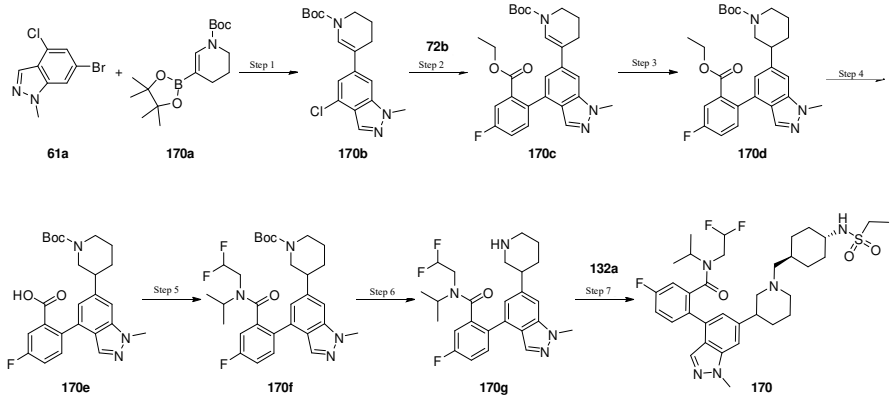
Step 7

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-6-({1-[(1*S*,3*S*,4*R*)-5-methylene-2-azabicyclo[2.2.2]octan-3-carbonyl]azacyclobutan-3-yl}methyl)-1*H*-indazole **169**

Compound **169e** (70 mg, 104.20 μmol) was dissolved in methane dioxide (2.0 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **169** (36.18 mg, 63.29 μmol, yield: 60.74 %) as white solid.
MS m/z (ESI): 572.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 – 7.73 (m, 1H), 7.66 – 7.51 (m, 2H), 7.47 – 7.26 (m, 2H), 6.99 – 6.82 (m, 1H), 4.96 – 4.85 (m, 1H), 4.68 (s, 1H), 4.34 – 4.14 (m, 2H), 4.09 – 4.02 (m, 3H), 4.02 – 3.96 (m, 1H), 3.81 (s, 1H), 3.76 – 3.36 (m, 4H), 3.06 (s, 2H), 3.02 – 2.65 (m, 5H), 2.47 – 2.34 (m, 3H), 2.29 – 2.06 (m, 2H), 1.69 – 1.60 (m, 2H), 1.44 – 1.36 (m, 2H), 1.25 – 1.09 (m, 1H), 1.01 – 0.94 (m, 1H), 0.47 – 0.10 (m, 1H).

Example 170

N-(2,2-difluoroethyl)-5-fluoro-2-[1-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **170**



Step 1

5-(4-chloro-1-methyl-1*H*-indazol-6-yl)-1,2,3,4-tetrahydropyridin-1-tert-butyl formate **170b**

Compound **61a** (500 mg, 2.04 mmol) was dissolved in dioxane (6.0 mL) and water (1.0 mL). Sodium carbonate (647.59 mg, 6.11 mmol), 5-(tetramethyl-1,3,2-dioxaboran-2-yl)- 1,2,3,4-tetrahydropyridin-1-tert-butyl formate **170a** (692.72 mg, 2.24 mmol) and Pd(dppf)Cl_2 (149.02 mg, 203.66 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (100 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **170b** (700 mg, 2.01 mmol, yield: 98.81%) as yellow solid.
MS m/z (ESI): 348.1 [M+1]

Step 2

5-{4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}-1,2,3,4-tetrahydropyridin-1-tert-butyl formate **170c**

Compound **170b** (400 mg, 1.15 mmol) and Compound **72b** (676.46 mg, 2.30 mmol) were dissolved in dioxane (12 mL) and water (2.0 mL). Cesium carbonate (1.08 g, 3.45 mmol) and Pd(dtbpf)Cl_2 (74.95 mg, 115.00 μmol) were added, and the mixture was stirred at 90°C under a nitrogen atmosphere to allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **170c** (490 mg, 1.02 mmol, yield: 88.86%) as yellow oil.
MS m/z (ESI): 480.3 [M+1]

Step 3

3-{4-[2-(ethoxycarbonyl)-4-fluorophenyl]-1-methyl-1*H*-indazol-6-yl}piperidin-1-tert-butyl formate **170d**

Compound **170c** (490 mg, 1.02 mmol) were dissolved in methanol (10.0 mL), followed by the addition of Pd/C (620.52 mg, 5.11 mmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at 50℃ for 12 hours. The reaction mixture was filtered through diatomite, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **170d** crude product of (477 mg, 990.54 μmol, yield: 96.94%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 482.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.69 – 7.62 (m, 2H), 7.45 (dd, J = 5.4, 8.4 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.23 (s, 1H), 6.92 (s, 1H), 4.08 (s, 3H), 3.50 (s, 2H), 2.87 (d, J = 5.2 Hz, 3H), 2.12 (br d, J = 13.0 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.65 – 1.62 (m, 2H), 1.48 (s, 9H), 0.88 – 0.79 (m, 3H).

Step 4

2-(6-{1-[(tert-butoxy)carbonyl]piperidin-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluorobenzoic acid **170e**

Compound **170d** (477 mg, 990.54 μmol) was dissolved in ethanol (10 mL), tetrahydrofuran (10 mL) and water (5.0 mL), followed by the addition of $LiOH.H_2O$ (71.16 mg, 2.97 mmol), and the mixture was stirred at 50°Cto allow for reacting for 12 hours. The mixture was cooled to room temperature, followed by removing the organic solvent under a reduced pressure. The mixture was regulated to PH ≤ 7 by adding 1M HCl, and extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **170e** (449 mg, 990.07 μmol, yield: 99.95%) as yellow solid was obtained. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 454.2 [M+1]

Step 5

3-(4-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)piperidin-1-tert-butyl carboxylate **170f**

Compound **170e** (150 mg, 330.76 μmol), Compound **94b** (79.19 mg, 496.14 μmol, hydrochloride) and 2-chloro-1-methylpyridinium iodide (109.85 mg, 429.98 μmol) were dissolved in DMF(1.88 mL), followed by the addition of DIPEA (128.24 mg, 992.27 μmol). The reaction mixture was stirred at room temperature for 1.0 hours. Ethyl acetate (20 mL) was added to the reaction mixture, which was then washed with water (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **170f** (87.6 mg, 156.81 μmol, yield: 47.4%) as yellow solid.

MS m/z (ESI): 559.3 [M+1]

Step 6

N-(2,2-difluoroethyl)-5-fluoro-2-[1-methyl-6-(piperidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **170g**

Compound **170f** (35 mg, 62.65 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **170g** (28.73 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 459.2 [M+1]

Step 7

N-(2,2-difluoroethyl)-5-fluoro-2-[1-methyl-6-(1-{[(1*r*,4*r*)-4-ethanesulfonamidocyclohexyl]methyl}piperidin-3-yl)-1*H*-indazol-4-yl]-*N*-(isopropyl)benzamide **170**

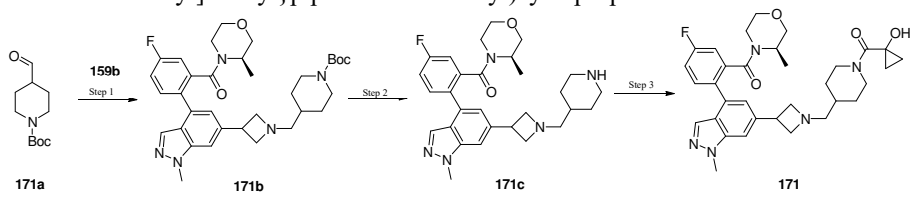
The crude product of Compound **170g** (28.73 mg), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(12.10 mg, 55.20 μmol) and triethylamine (15.23 mg, 150.54 μmol) were dissolved in methanol (2.0 mL), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (6.31 mg, 100.36 μmol) was added, and the mixture was stirred at room temperature for 1.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/tetrahydrofuran as an elution system, to obtain the title Compound **170** (9.69 mg, 14.64 μmol, yield: 29.18%) as white solid.

MS m/z (ESI): 662.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 0.8 Hz, 1H), 7.49 (ddd, J = 1.0, 5.4, 8.6 Hz, 1H), 7.34 (s, 1H), 7.24 (dt, J = 2.6, 8.4 Hz, 1H), 7.13 (td, J = 2.2, 8.6 Hz, 1H), 6.93 (s, 1H), 5.79 – 5.44 (m, 1H), 4.44 (s, 1H), 3.94 (s, 3H), 3.55 – 3.38 (m, 2H), 3.14 – 2.94 (m, 2H), 2.93 – 2.83 (m, 4H), 2.14 (t, J = 6.6 Hz, 2H), 2.08 – 1.94 (m, 2H), 1.90 – 1.80 (m, 3H), 1.78 – 1.65 (m, 3H), 1.55 – 1.34 (m, 3H), 1.19 – 1.13 (m, 6H), 0.95 – 0.84 (m, 2H), 0.77 (d, J = 6.4 Hz, 3H), -0.01 (d, J= 6.8 Hz, 2H).

Example 171

1-(4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-carbonyl)cyclopropan-1-ol **171**



Step 1

4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-tert-butyl formate **171b**

The crude product of Compound **159b** (226.01 mg, 432.57 μmol, trifluoroacetate), 4-formylpiperidin-1-tert-butyl formate **171a** (110.71 mg, 519.08 μmol) and triethylamine (87.54 mg, 865.14 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 30 min. Sodium cyanoborohydride (81.55 mg, 1.30 mmol) was added, and the reaction mixture was stirred at room temperature for 12 hour. Acetic acid (50 mg) was added to the reaction mixture, which was then warmed to 50°C and further stirred for 3.0 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **171b** (200 mg, 330.17 μmol, yield: 76.33%) as faint yellow solid.

MS m/z (ESI): 606.3 [M+1]

Step 2

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-6-{1-[(piperidin-4-yl)methyl]azacyclobutan-3-yl}-1*H*-indazole **171c**

Compound **171b** (65 mg, 107.31 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **171c** (54.3 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 506.3 [M+1]

Step 3

1-(4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-carbonyl)cyclopropan-1-ol **171**

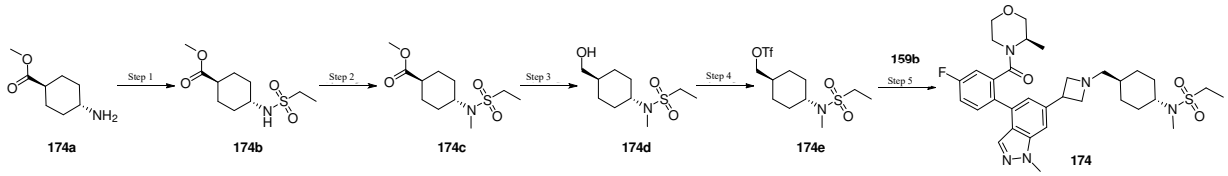
1-Hydroxylcyclopropan-1-carboxylic acid (12.05 mg, 118.04 μmol), triethylamine (32.58 mg, 321.94 μmol) and HATU(81.61 mg, 214.63 μmol) were dissolved in dichloromethane (5.0 mL), and stirred at room temperature for 30 min, followed by the addition of the crude product of Compound **171c** (54.3 mg). The reaction mixture was stirred at room temperature for 2 hours. 1-Hydroxylcyclopropan-1-carboxylic acid (12.05 mg, 118.04 μmol) and HATU(81.61 mg, 214.63 μmol) were supplemented, and the mixture was further stirred for 4.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 23%-53%), to obtain the title Compound **171** (8.88 mg, 15.06 μmol, yield: 14.03 %) as white solid.

MS m/z (ESI): 590.3 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 1H), 7.64 – 7.51 (m, 1H), 7.41 – 7.28 (m, 2H), 7.26 – 7.09 (m, 2H), 4.61 – 4.28 (m, J = 13.1 Hz, 3H), 4.12 (s, 3H), 3.92 – 3.82 (m, 3H), 3.68 – 3.38 (m, 2H), 3.37 – 3.14 (m, 3H), 3.13 – 2.95 (m, 1H), 2.88 – 2.79 (m, 2H), 2.63 – 2.35 (m, 3H), 1.86 – 1.79 (m, 2H), 1.72 – 1.39 (m, 2H), 1.34 – 1.19 (m, 4H), 1.13 – 1.04 (m, 3H), 0.99 – 0.91 (m, 2H), 0.62 – 0.14 (m, 1H).

Example 174

N-methyl-*N*-[(1*r*,4*r*)-4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **174**



Step 1

(1*r*,4*r*)-4-ethanesulfonamidocyclohexan-1-methyl carboxylate **174b**

(1*r*,4*r*)-4-aminocyclohexan-1-methyl carboxylate **174a** (1.86 g, 9.63 mmol, hydrochloride) was dissolved in dichloromethane (20 mL), and the mixture was cooled to 5°C in an ice-water bath. Triethylamine (1.95 g, 19.26 mmol) was added, followed by the slow dropwise addition of ethylsulfonyl chloride (1.24 g, 9.63 mmol). The reaction mixture was stirred at room temperature for 2 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **174b** (1.23 g, 4.93 mmol, yield: 51.23%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (br d, J = 8.0 Hz, 1H), 3.68 (s, 3H), 3.25 (m, 1H), 3.05 (q, J = 7.4 Hz, 2H), 2.29 – 2.20 (m, 1H), 2.17 – 2.10 (m, 2H), 2.08 – 2.00 (m, 2H), 1.61 – 1.48 (m, 2H), 1.38 (t, J = 7.4 Hz, 3H), 1.34 – 1.21 (m, 2H).

Step 2

(1*r*,4*r*)-4-(*N*-methylethanesulfonamido)cyclohexan-1-methyl carboxylate **174c**

Compound **174b** (500 mg, 1.90 mmol) was dissolved in DMF(20 mL), followed by the addition of potassium carbonate (787.19 mg, 5.70 mmol) and iodomethane (1.08 g, 7.59 mmol) at 25°C. The reaction mixture was stirred at 50°C to allow for reacting for 12 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **174c** (260 mg, 987.27 μmol, yield: 52%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (m, 4H), 2.90 (q, J = 7.4 Hz, 2H), 2.72 (s, 3H), 2.18 – 2.08 (m, 1H), 2.02 (br d, J = 7.4 Hz, 2H), 1.81 – 1.73 (m, 2H), 1.55 – 1.45 (m, 4H), 1.27 (t, J = 7.4 Hz, 3H).

Step 3

N-methyl-*N*-[(1*r*,4*r*)-4-(hydroxymethyl)cyclohexyl]ethan-1-sulfonamide **174d**

Compound **174c** (260 mg, 987.27 μmol) was dissolved in dichloromethane (7.7 mL), and cooled to 0°C, followed by the addition of DIBAL-H(1 M, 2.47 mL). The mixture was stirred at 0°C to allow for reacting for 1.0 hour, sodium sulfate decahydrate (5.0 g) was added, and the reaction mixture was further stirred for 15 min, then warmed to room temperature, and stirred for 0.5 hours. The mixture was filtered, and the organic phase was collected and concentrated under a reduced pressure . The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **174d** (128 mg, 543.89 μmol, yield: 55.1%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 – 3.62 (m, 1H), 3.47 (d, J = 6.4 Hz, 2H), 2.97 (q, J = 7.4 Hz, 2H), 2.81 (s, 3H), 1.93 – 1.80 (m, 4H), 1.63 – 1.50 (m, 4H), 1.43 (m, 2H), 1.35 (t, J = 7.4 Hz, 3H).

Step 4

[(1*r*,4*r*)-4-(*N*-methylethanesulfonamido)cyclohexyl]methyl trifluoromethanesulfonate

Compound **174d** (128 mg, 543.89 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (110.07 mg, 1.09 mmol). The reaction mixture was cooled to -78°C, followed by dropwise adding the solution of trifluoromethanesulfonic anhydride (199.49 mg, 707.05 μmol) in dichloromethane (3.0 mL) slowly. The reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was directly used in the next step of reaction without treatment.

Step 5

N-methyl-*N*-[(1*r*,4*r*)-4-{[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **174**

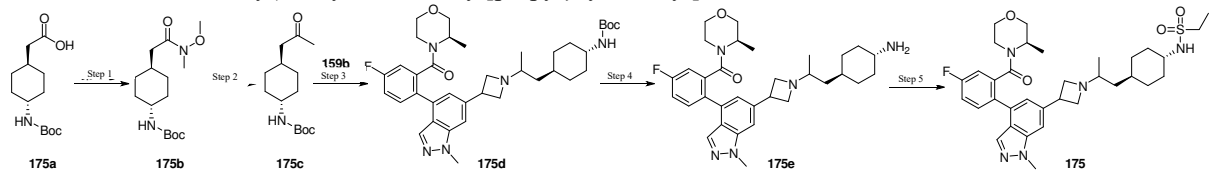
Compound **159b** (120 mg, 293.78 μmol) was dissolved in dichloromethane (10 mL), and cooled to 0°C, followed by the slow dropwise addition of the mixture from the previous step of reaction. After drowpise addition, the mixture was stirred at room temperature for 12 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **174** (41.5 mg, 66.32 μmol, yield: 22.57%) as yellow solid.

MS m/z (ESI): 626.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.93 – 7.87 (m, 1H), 7.69 (td, J = 5.2, 8.8 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.43 – 7.28 (m, 2H), 7.26 – 7.10 (m, 1H), 4.27 – 4.15 (m, 3H), 4.13 – 4.10 (m, 3H), 3.99 – 3.70 (m, 3H), 3.68 – 3.54 (m, 2H), 3.54 – 3.35 (m, 2H), 3.25 – 3.09 (m, 2H), 3.04 (q, J = 7.4 Hz, 3H), 2.79 (s, 3H), 1.96 – 1.88 (m, 2H), 1.83 – 1.76 (m, 2H), 1.66 (dq, J = 3.6, 12.8 Hz, 3H), 1.32 – 1.27 (m, 4H), 1.26 – 1.11 (m, 4H), 1.08 (d, J = 6.8 Hz, 1H), 0.48 (d, J = 6.8 Hz, 1H).

Example 175

N-[(1*r*,4*r*)-4-{2-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]propyl}cyclohexyl]ethan-1-sulfonamide **175**



Step 1

N-[(1*r*,4*r*)-4-{[methoxy(methyl)aminoformyl]methyl}cyclohexyl]tert-butyl carbamate **175b**

2-[(1*r*,4*r*)-4-{[(tert-butoxy)carbonyl]amino}cyclohexyl]acetic acid **175a** (500 mg, 1.94 mmol) and triethylamine (589.85 mg, 5.83 mmol) were dissolved in dichloromethane (8.0 mL), followed by the addition of EDCI (744.98 mg, 3.89 mmol) and HOBt (525.11 mg, 3.89 mmol), and the mixture was stirred at room temperature for 30 min, followed by the addition of N-methoxymethylamine (227.44 mg, 2.33 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 12 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **175b** (525 mg, 1.75 mmol, yield: 89.95%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 1H), 3.67 (s, 3H), 3.46 – 3.30 (m, 1H), 3.18 (s, 3H), 2.31 (m, 2H), 1.99 (m, 2H), 1.81 (m, 3H), 1.44 (s, 9H), 1.21 – 1.00 (m, 4H).

Step 2

N-[(1*r*,4*r*)-4-(2-oxopropyl)cyclohexyl]tert-butyl carbamate

Compound **175b** (525 mg, 1.75 mmol) was dissolved in tetrahydrofuran (19.94 mL), and cooled to 0°C, followed by the addition of a methylmagnesium bromide tetrahydrofuran solution (3 M, 640.83 μL). The reaction mixture was stirred at room temperature for 12 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the crude product of title Compound **175c** (82 mg, 321.13 μmol, yield: 18.37%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.32 (m, 1H), 3.44 – 3.30 (m, 1H), 2.32 (d, J = 6.4 Hz, 2H), 2.13 (s, 3H), 2.03 – 1.95 (m, 2H), 1.79 – 1.71 (m, 3H), 1.44 (s, 9H), 1.19 – 0.95 (m, 4H).

Step 3

N-[(1*r*,4*r*)-4-{2-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]propyl}cyclohexyl]tert-butyl carbamate **175d**

Compound **159b** (100 mg, 244.82 μmol) and Compound **175c** (68.77 mg, 269.30 μmol) were dissolved in methanol (10 mL), followed by the addition of zinc dichloride (100.10 mg, 734.45 μmol), and the mixture was stirred at 60°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (46.15 mg, 734.45 μmol) and stirring at 60°C for 4.0 hours. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then stirred for 0.5 hours and extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **175d** (90 mg, 138.93 μmol, yield: 56.75%) as white solid.

MS m/z (ESI): 648.6 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.84 (m, 1H), 7.74 – 7.54 (m, 1H), 7.44 – 7.28 (m, 2H), 7.27 – 7.13 (m, 2H), 4.56 – 4.00 (m, 8H), 3.92 – 3.34 (m, 5H), 3.25 – 2.74 (m, 4H), 2.58 – 2.19 (m, 2H), 2.09 – 1.76 (m, 4H), 1.45 (s, 9H), 1.38 – 1.26 (m, 4H), 1.22 – 1.17 (m, 2H), 1.14 – 0.96 (m, 4H), 0.58 – 0.05 (m, 2H).

Step 4

(1*r*,4*r*)-4-{2-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]propyl}cyclohexan-1-amine **175e**

Compound **175d** (90 mg, 138.93 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of

trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a saturated aqueous sodium bicarbonate solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **175e** (65 mg, 118.68 μmol, yield: 85.42%) was obtained as white solid.

MS m/z (ESI): 548.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.84 (m, 1H), 7.68 – 7.28 (m, 3H), 7.23 – 6.95 (m, 2H), 4.80 – 4.22 (m, 4H), 4.13 (s, 3H), 3.95 – 3.39 (m, 5H), 3.14 – 2.78 (m, 4H), 2.55 – 2.34 (m, 2H), 2.29 – 2.08 (m, 4H), 2.04 – 1.99 (m, 2H), 1.35 – 1.29 (m, 8H), 1.22 – 1.19 (m, 2H), 0.89 (br s, 2H).

Step 5

N-[(1*r*,4*r*)-4-{2-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]propyl}cyclohexyl]ethan-1-sulfonamide **175**

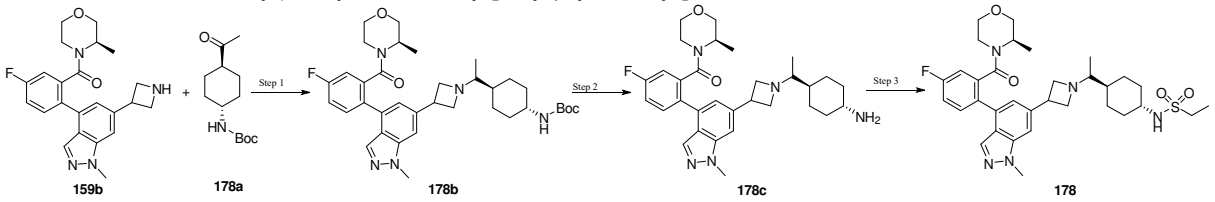
The crude product of Compound **175e** (65 mg, 118.68 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (24.02 mg, 237.35 μmol), cooling to 0°C, and the slow dropwise addition of the dichloromethane solution (1 mL) of ethanesulfonyl chloride (19.84 mg, 154.28 μmol), and the mixture was stirred at room temperature for 12 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **175** (44.33 mg, 69.28 μmol, yield: 58.38 %) as white solid.

MS m/z (ESI): 640.4[M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 1H), 7.69 – 7.52 (m, 1H), 7.40 – 7.28 (m, 1H), 7.27 – 7.01 (m, 3H), 4.60 – 4.23 (m, 1H), 4.12 (s, 3H), 4.11 – 4.05 (m, 1H), 3.99 – 3.86 (m, 3H), 3.67 – 3.10 (m, 6H), 3.09 – 2.95 (m, 3H), 2.88 – 2.75 (m, 1H), 2.64 – 2.32 (m, 3H), 2.13 – 2.00 (m, 2H), 1.97 – 1.73 (m, 2H), 1.48 – 1.33 (m, 4H), 1.32 – 1.24 (m, 4H), 1.17 – 1.05 (m, 3H), 1.03 – 0.92 (m, 3H), 0.62 – 0.14 (m, 1H).

Example 178

N-[(1*r*,4*r*)-4-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]ethyl}cyclohexyl]ethan-1-sulfonamide **178**



Step 1

N-[(1*r*,4*r*)-4-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]ethyl}cyclohexyl]tert-butyl carbamate **178b**

Compound **159b** (100 mg, 244.82 μmol), (4-acetylcyclohexyl)tert-butyl carbamate **178a** (88.62 mg, 367.23 μmol) and zinc chloride (66.74 mg, 489.63 μmol) were dissolved in methanol (2.0 mL), and stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (46.15 mg, 734.45 μmol) was added, and the mixture was further stirred at 50℃ for 3.0 hours. The reaction mixture was cooled to room temperature, followed by adding a saturated aqueous sodium bicarbonate solution (10 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate/ethanol as an elution system, to obtain the title Compound **178b** (138 mg, 217.74 μmol, yield: 88.94 %) as faint yellow solid.

MS m/z (ESI): 634.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (s, 1H), 7.77 – 7.48 (m, 2H), 7.42 – 7.05 (m, 3H), 4.63 – 4.20 (m, 1H), 4.16 – 4.06 (m, 3H), 3.97 – 3.34 (m, 7H), 3.27 – 2.81 (m, 4H), 2.54 – 2.30 (m, 2H), 2.22 – 1.48 (m, 6H), 1.45 – 1.39 (m, 9H), 1.29 – 1.21 (m, 3H), 1.19 – 1.11 (m, 2H), 1.09 – 1.04 (m, 1H), 0.98 – 0.90 (m, 3H), 0.51 – 0.18 (m, 1H).

Step 2

(1*r*,4*r*)-4-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]ethyl}cyclohexan-1-amine **178c**

Compound **178b** (120 mg, 189.34 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over

anhydrous sodium sulfate, concentrated under a reduced pressure and lyophilized, to obtain the crude product of title Compound **178c** (122.64 mg, 229.80 μmol, yield: 121.37%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 534.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.63 – 7.47 (m, 1H), 7.46 – 7.41 (m, 1H), 7.31 – 7.24 (m, 1H), 7.21 – 6.96 (m, 2H), 4.39 – 4.12 (m, 1H), 4.03 – 3.99 (m, 3H), 3.79 – 3.70 (m, 3H), 3.50 – 3.29 (m, 2H), 3.18 – 3.10 (m, 2H), 2.88 – 2.74 (m, 1H), 2.71 – 2.59 (m, 1H), 2.43 – 2.23 (m, 2H), 1.94 – 1.86 (m, 2H), 1.72 – 1.33 (m, 6H), 1.15 – 1.06 (m, 4H), 0.99 – 0.94 (m, 1H), 0.81 – 0.79 (m, 3H), 0.42 – 0.07 (m, 1H).

Step 3

N-[(1*r*,4*r*)-4-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]ethyl}cyclohexyl]ethan-1-sulfonamide **178**

The crude product of Compound **178c** (102.19 mg, 157.78 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of triethylamine (47.90 mg, 473.34 μmol), cooling to 0°C, and the addition of ethanesulfonyl chloride (40.57 mg, 315.56 μmol), and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 5%-35%), to obtain the title Compound **178** (9.8 mg, 15.66 μmol, yield: 9.93%) as pink solid.

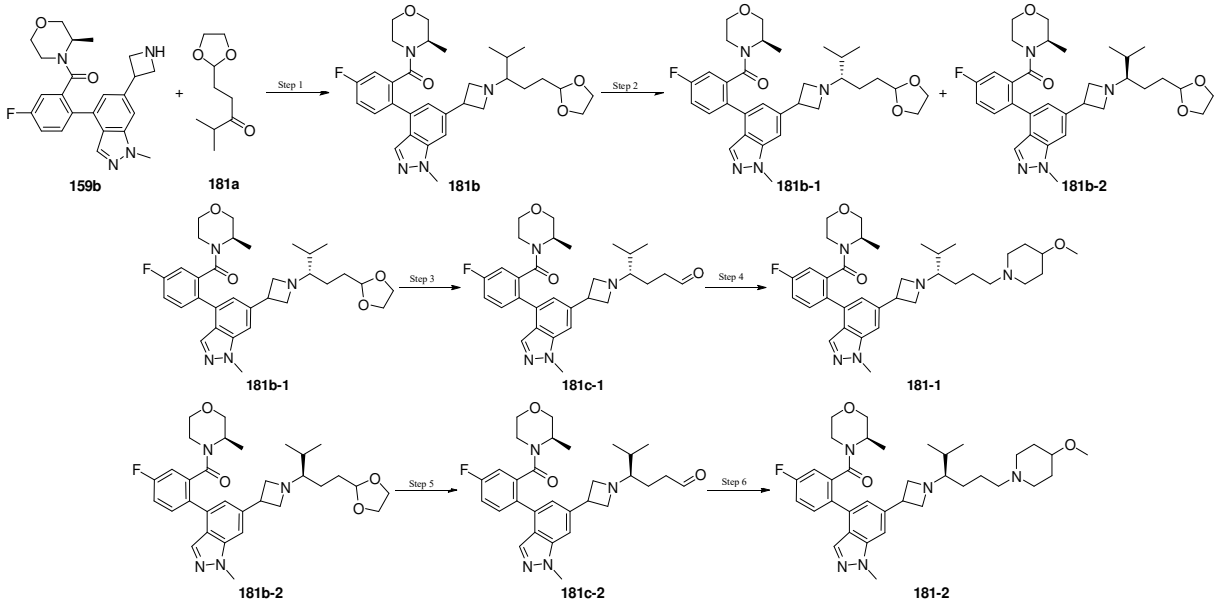
MS m/z (ESI): 626.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.71 – 7.51 (m, 2H), 7.48 – 7.26 (m, 2H), 7.20 – 6.90 (m, 2H), 4.34 – 3.99 (m, 4H), 3.78 (br s, 5H), 3.28 – 2.65 (m, 9H), 2.24 – 2.13 (m, 1H), 1.89 – 1.25 (m, 6H), 1.20 – 1.15 (m, 4H), 1.14 – 0.95 (m, 4H), 0.87 – 0.69 (m, 3H), 0.50 – 0.16 (m, 1H).

Examples 181-1 and 181-2

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-6-{1-[(3*S*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **181-1**

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **181-2**



Step 1

6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1H-indazole **181b**

Compound **159b** (513 mg, 1.26 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (237.92 mg, 1.38 mmol) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$ (513.53 mg, 3.77 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (157.85 mg, 2.51 mmol) and stirring at 50°C for 1.0 hour. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the

silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the reverse-phase C18 column chromatography (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 0%-50%), to obtain the title Compound **181b** (300 mg, 531.27 μmol, yield: 63.78%).
MS m/z (ESI): 565.3 [M+1]

Step 2

6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1H-indazole **181b-1**

6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1H-indazole **181b-2**

Compound **181b** (300 mg, 531.27 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol; elution gradient: 40%), to obtain the title Compounds **181b-1** (106 mg, 187.71 μmol, yield: 35.33%) and **181b-2** (92 mg, 162.92 μmol, yield: 30.67%).

Single-configuration Compound 181b-1:
MS m/z (ESI):565.3 [M+1]
Chiral HPLC analysis: retention time: 1.456 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 181b-2:
MS m/z (ESI):565.3 [M+1]
Chiral HPLC analysis: retention time: 1.670 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

(4*S*)-4-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexanal **181c-1**

Compound **181b-1** (190 mg, 336.47 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 12 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **181c-1** (180 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 181c-1:
MS m/z (ESI): 521.2 [M+1]

Step 4

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-6-{1-[(3*S*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **181-1**

The crude product of Compound **181c-1** (45 mg, 86.43 μmol) and 4-methoxypiperidine (10.95 mg, 95.08 μmol) were dissolved in methanol (5 mL), and stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (10.86 mg, 172.87 μmol) was added, allowing for reacting at room temperature for 4.0 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then stirred for 0.5 hours. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system. The title Compound **181-1** (19.86 mg, 32.04 μmol, yield: 37.07%) was obtained.

Single-configuration Compound 181-1:
MS m/z (ESI):620.4 [M+1]
Chiral SFC: retention time: 1.875 min; chromatographic column: Chiralpak IC-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH+ACN (0.05% DEA): elution gradient: 40%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.80 (m, 1H), 7.67 – 7.51 (m, 1H), 7.37 – 7.28 (m, 1H), 7.26 – 7.05 (m, 3H), 4.73 – 4.33 (m, 1H), 4.13 (s, 3H), 4.08 – 3.91 (m, 1H), 3.89 – 3.79 (m, 2H), 3.69 – 3.39 (m, 2H), 3.34 (s, 3H), 3.30 – 2.96 (m, 4H), 2.89 – 2.77 (m, 3H), 2.50 – 2.34 (m, 5H), 2.25 – 2.14 (m, 1H), 2.06 – 1.91 (m, 2H), 1.88 – 1.78 (m, 1H), 1.72 – 1.63 (m, 3H), 1.42 – 1.32 (m, 2H), 1.29 – 1.22 (m, 2H), 1.10 – 1.02 (m, 1H), 0.96 – 0.89 (m, 6H), 0.63 – 0.04 (m, 2H).

Step 5

(4*R*)-4-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexanal **181c-2**

Compound **181b-2** (180 mg, 318.76 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 12 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **181c-2** (180 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 181c-2:

MS m/z (ESI): 521.3 [M+1]

Step 6

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **181-2**

The crude product of Compound **181c-2** (45 mg, 86.43 μmol) and 4-methoxypiperidine (11.95 mg, 103.72 μmol) were dissolved in methanol (1.5 mL), followed by the addition of acetic acid (7.79 mg, 129.65 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (16.3 mg, 259.3 μmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 41%-71%) .The title Compound **181-2** (23.72 mg, 38.27 μmol, yield: 44.28%) was obtained.

Single-configuration Compound 181-2:

MS m/z (ESI):620.5 [M+1]

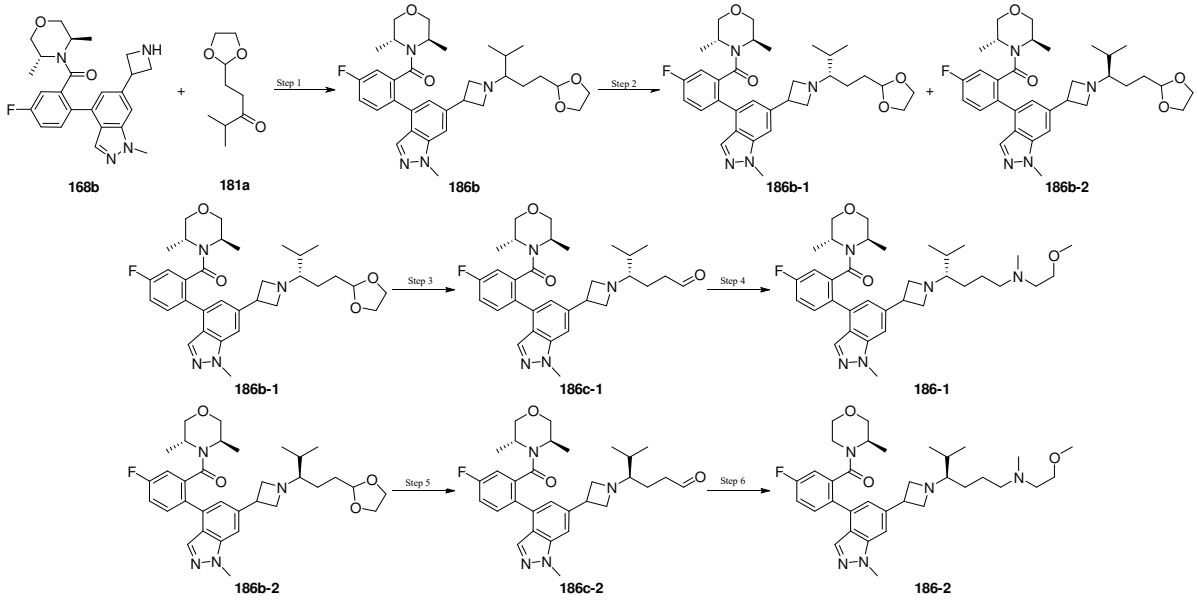
Chiral SFC: retention time: 1.170 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.78 – 7.67 (m, 1H), 7.55 – 7.40 (m, 1H), 7.39 – 7.28 (m, 1H), 7.25 – 7.09 (m, 2H), 7.08 – 6.91 (m, 1H), 4.31 – 4.07 (m, 1H), 3.96 – 3.89 (m, 3H), 3.83 – 3.61 (m, 4H), 3.48 – 3.33 (m, 1H), 3.27 – 3.13 (m, 5H), 3.07 – 2.68 (m, 3H), 2.66 – 2.55 (m, 2H), 2.39 – 2.22 (m, 1H), 2.22 – 2.14 (m, 2H), 2.12 – 1.99 (m, 3H), 1.79 – 1.68 (m, 3H), 1.33 (s, 7H), 1.09 – 1.05 (m, 1H), 0.92 – 0.88 (m, 1H), 0.82 – 0.73 (m, 6H), 0.37 - -0.01 (m, 1H).

Examples 186-1 and 186-2

[(4*S*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl](2-methoxyethyl)methylamine **186-1**

[(4*R*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl](2-methoxyethyl)methylamine **186-2**



Step 1

4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-6-{1-[1-(dioxolan-2-yl)-4-methylpentan-3-yl]methylpentan-3-yl}-1-methyl-1H-indazole **186b**

Compound **168b** (3.49 g, 8.26 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (1.56 g, 9.09 mmol)

were dissolved in methanol (20 mL), followed by the addition of $ZnCl_2$ (3.38 g, 24.78 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (1.04 g, 16.52 mmol) and stirring at 50°C for 13 hour. A saturated aqueous sodium carbonate solution (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **186b** (3.89 g, 6.72 mmol, yield: 81.37%) as yellow solid.
MS m/z (ESI): 579.3 [M+1]

Step 2

4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-6-{1-[(3*S*)-1-(dioxolan-2-yl)-4-methylpentan-3-yl]methylpentan-3-yl}-1-methyl-1H-indazole **186b-1**

4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-6-{1-[(3*R*)-1-(dioxolan-2-yl)-4-methylpentan-3-yl]methylpentan-3-yl}-1-methyl-1H-indazole **186b-2**

Compound **186b** (3.89 g, 6.72 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IG (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-ethanol (0.1% ammonia water); elution gradient: 40%), to obtain the title Compounds **186b-1** (1.45 g, 2.51 mmol, yield: 37.28%) and **186b-2** (1.89 g, 3.27 mmol, yield: 48.59%).

Single-configuration Compound 186b-1:
MS m/z (ESI):579.1 [M+1]
Chiral HPLC analysis: retention time: 1.168 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 40%.

Single-configuration Compound 186b-2:
MS m/z (ESI):579.2 [M+1]
Chiral HPLC analysis: retention time: 0.738 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 40%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.50 (dd, J = 5.7, 7.9 Hz, 1H), 7.34 (s, 1H), 7.27 – 7.21 (m, 2H), 7.11 – 6.97 (m, 1H), 4.84 (t, J = 4.5 Hz, 1H), 4.13 (s, 3H), 3.97 – 3.94 (m, 2H), 3.86 – 3.82 (m, 2H), 3.80 – 3.62 (m, 2H), 3.51 – 3.32 (m, 2H), 3.09 – 2.96 (m, 1H), 2.70 – 2.54 (m, 1H), 2.44 – 2.15 (m, 2H), 2.02 – 1.83 (m, 2H), 1.80 – 1.71 (m, 3H), 1.67 – 1.40 (m, 4H), 1.04 (s, 3H), 0.98 (d, J = 6.6 Hz, 6H), 0.87 (s, 3H).

Step 3

(4*S*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexanal **186c-1**

Compound **186b-1** (153 mg, 264.38 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a saturated aqueous sodium carbonate solution (10 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **186c-1** (140 mg, 261.85 μmol, yield: 99.04%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 186c-1:
MS m/z (ESI): 535.3 [M+1]

Step 4

[(4*S*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl](2-methoxyethyl)methylamine **186-1**

The crude product of Compound **186c-1** (140 mg, 261.85 μmol) and 2-methoxy-N-methyl-ethylamine (35.01 mg, 392.77 μmol) was dissolved in methanol (2 mL), and stirred at room temperature for 1.0 hour under the protection of nitrogen. Acetic acid (15.72 mg, 261.85 μmol) and sodium cyanoborohydride (49.36 mg, 785.54 μmol) were added, allowing for reacting at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 0%-30%), to obtain the title Compound **186-1** (73.28 mg, 120.57 μmol, yield: 46.04%).

Single-configuration Compound 186-1:
MS m/z (ESI):608.4 [M+1]
Chiral SFC: retention time: 1.101 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 – 7.29 (m, 5H), 7.12 – 6.90 (m, 1H), 4.08 – 4.04 (m, 3H), 3.80 – 3.71 (m,

3H), 3.61 – 3.48 (m, 2H), 3.46 – 3.39 (m, 2H), 3.32 – 2.99 (m, 7H), 2.62 – 2.54 (m, 2H), 2.53 – 2.47 (m, 3H), 2.44 – 2.37 (m, 2H), 2.26 – 2.15 (m, 4H), 1.84 – 1.71 (m, 1H), 1.54 – 1.41 (m, 2H), 1.34 – 1.15 (m, 2H), 1.05 – 0.55 (m, 11H).

Step 5

(4*R*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexanal **186c-2**

Compound **186b-2** (1.89 g, 3.27 mmol) was dissolved in acetonitrile (20 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 20 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 12 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **186c-2** (1.34 g, 2.51 mmol, yield: 76.74%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 186c-2:

MS m/z (ESI): 535.2 [M+1]

Step 6

[(4*R*)-4-[3-(4-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl](2-methoxyethyl)methylamine **186-2**

Compound **186c-2** (150 mg, 280.55 μmol) and 2-methoxy-N-methyl-ethylamine (37.51 mg, 420.83 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (16.85 mg, 280.55 μmol), and the mixture was stirred at room temperature for 1.0 hour.Sodium cyanoborohydride (52.89 mg, 841.65 μmol) was added, allowing for reacting at room temperature for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 46%-76%). The title Compound **186-2** (100 mg, 164.53 μmol, yield: 58.64%) was obtained.

Single-configuration Compound 186-2:

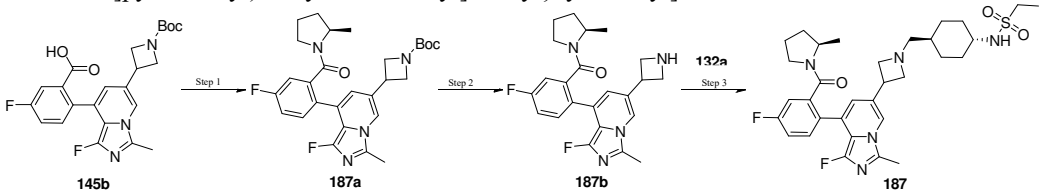
MS m/z (ESI):608.5 [M+1]

Chiral SFC: retention time: 0.959 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (s, 1H), 7.64 – 7.51 (m, 2H), 7.43 – 7.28 (m, 2H), 7.09 (s, 1H), 4.13 (s, 3H), 3.98 – 3.79 (m, 4H), 3.77 – 3.63 (m, 2H), 3.52 (t, J = 5.6 Hz, 2H), 3.37 – 3.33 (m, 5H), 3.12 (d, J = 10.0 Hz, 1H), 2.61 (t, J = 5.6 Hz, 3H), 2.43 (t, J = 7.8 Hz, 2H), 2.35 (d, J = 9.2 Hz, 1H), 2.29 (s, 3H), 2.25 (q, J = 4.4 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.66 – 1.54 (m, 2H), 1.47 – 1.37 (m, 1H), 1.36 – 1.26 (m, 1H), 1.08 (d, J = 4.8 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.74 (s, 3H).

Example 187

N-[(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(2*R*)-2-methylpyrrolidin-1-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **187**



Step 1

3-(1-fluoro-8-{4-fluoro-2-[(2*R*)-2-methylpyrrolidin-1-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **187a**

Compound **145b** (318 mg, 717.12 μmol), triethylamine (217.69 mg, 2.15 mmol) and HATU(327.20 mg, 860.54 μmol) were dissolved in dichloromethane (5.0 mL), and stirred at room temperature for 10 min, followed by the addition of (2*R*)-2-methylpyrrolidine (73.27 mg, 860.54 μmol). The reaction mixture was stirred at 25℃ for 12 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **187a** (340 mg, 665.92 μmol, yield: 92.86%) as yellow solid.

MS m/z (ESI): 511.2 [M+1]

Step 2

(2*R*)-1-{2-[6-(azacyclobutan-3-yl)-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-2-methylpyrrolidine **187b**

Compound **187a** (210 mg, 411.30 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with dichloromethane (10 mL), and regulated to PH = 11 with 10% aqueous NaOH solution, the mixture was extracted with dichloromethane (15 mL×3), and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the crude product of title Compound **187b** (200 mg, 487.26 μmol, yield: 118.47%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 411.2 [M+1]

Step 3

N-[(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(2*R*)-2-methylpyrrolidin-1-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **187**

The crude product of Compound **187b** (96.46 mg, 183.91 μmol), *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(48.40 mg, 220.69 μmol) and triethylamine (55.83 mg, 551.73 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (26.79 mg, 426.33 μmol) was added, and the mixture was stirred at room temperature for 11 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 14%-44%), to obtain the title Compound **187** (39.33 mg, 64.08 μmol, yield: 34.84 %) as yellow solid.

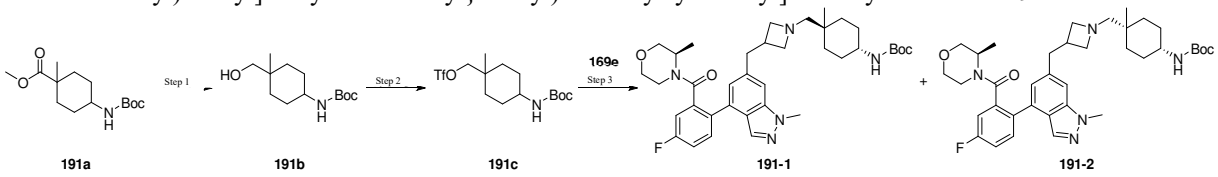
MS m/z (ESI): 614.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.21 – 8.11 (m, 1H), 7.83 (s, 1H), 7.57 – 7.48 (m, 1H), 7.42 – 7.29 (m, 2H), 7.02 – 6.95 (m, 1H), 6.73 – 6.57 (m, 1H), 3.98 – 3.89 (m, 1H), 3.61 – 3.51 (m, 3H), 3.18 – 3.04 (m, 3H), 3.00 – 2.92 (m, 3H), 2.54 (s, 3H), 2.34 – 2.26 (m, 2H), 1.93 – 1.69 (m, 5H), 1.66 – 1.47 (m, 2H), 1.42 – 1.30 (m, 1H), 1.24 – 1.11 (m, 6H), 0.99 – 0.75 (m, 5H).

Examples 191-1 and 191-2

N-[(4*r*)-4-({3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-yl}methyl)-4-methylcyclohexyl]tert-butyl carbamate **191-1**

N-[(4*s*)-4-({3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-yl}methyl)-4-methylcyclohexyl]tert-butyl carbamate **191-2**



Step 1

N-[4-(hydroxymethyl)-4-methylcyclohexyl]tert-butyl carbamate **191b**

4-{[(Tert-butoxy)carbonyl]amino}-1-methylcyclohexan-1-methyl carboxylate **191a** (770 mg, 2.84 mmol) was dissolved in THF (8.3 mL), and cooled to 0°C under a nitrogen atmosphere, followed by the slow addition of $LiAlH_4$ (161.55 mg, 4.26 mmol), and the mixture was stirred at room temperature for 12 hours. Ethyl acetate was added to quench the reaction, the reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **191b** (230 mg, 945.17 μmol, yield: 33.31%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.77 – 7.48 (m, 2H), 7.42 – 7.05 (m, 3H), 4.63 – 4.20 (m, 1H), 4.16 – 4.06 (m, 3H), 3.97 – 3.34 (m, 7H), 3.27 – 2.81 (m, 4H), 2.54 – 2.30 (m, 2H), 2.22 – 1.48 (m, 6H), 1.45 – 1.39 (m, 9H), 1.29 – 1.21 (m, 3H), 1.19 – 1.11 (m, 2H), 1.09 – 1.04 (m, 1H), 0.98 – 0.90 (m, 3H), 0.51 – 0.18 (m, 1H).

Step 2

N-{4-methyl-4-[(trifluoromethanesulfonyloxy)methyl]cyclohexyl}tert-butyl carbamate **191c**

Compound **191b** (230 mg, 945.17 μmol) was dissolved in dichloromethane (4.0 mL), followed by the addition of triethylamine (143.46 mg, 1.42 mmol) at 25°C. The reaction mixture was cooled to -78°C, followed by dropwise adding the solution of trifluoromethanesulfonic anhydride (346.67 mg, 1.23 mmol) in dichloromethane (3 mL) slowly. After dropwise addition, the reaction mixture was warmed to 0°C, and stirred to allow for reacting for 1.0 hour. The reaction mixture was directly used in the next step of reaction without treatment.

Step 3

N-[(4*r*)-4-({3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-yl}methyl)-4-methylcyclohexyl]tert-butyl carbamate **191-1**

N-[(4*s*)-4-({3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)methyl]azacyclobutan-1-yl}methyl)-4-methylcyclohexyl]tert-butyl carbamate **191-2**

The solution (2 mL) of Compound **191c** resulting from the previous step of reaction was cooled to 0°C, followed by the dropwise addition of triethylamine (19.16 mg, 189.35 μmol) and the dichloromethane solution (1.0 mL) of Compound **169e**(80 mg, 189.35 μmol). The reaction mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 24%-44%), to obtain the title Compounds **191-1** (1.01 mg, 1.56 μmol, yield: 0.8%) and **191-2** (1.6 mg, 2.47 μmol, yield: 1.3%).

Single-configuration Compound 191-1:

MS m/z (ESI):648.3 [M+1]

HPLC: retention time: 3.232 min.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 0.54H), 7.87 – 7.73 (m, 1H), 7.64 – 7.29 (m, 4H), 6.95 – 6.77 (m, 1H), 4.34 – 3.99 (m, 4H), 3.59 – 3.48 (m, 1H), 3.04 – 2.84 (m, 7H), 2.70 – 2.66 (m, 1H), 2.63 (s, 3H), 2.36 – 2.26 (m, 4H), 2.07 (s, 2H), 1.80 – 1.73 (m, 2H), 1.59 – 1.48 (m, 2H), 1.46 – 1.41 (m, 1H), 1.38 (s, 9H), 1.26 – 1.17 (m, 2H), 1.15 – 1.10 (m, 1H), 1.02 – 0.78 (m, 4H), 0.46 – 0.13 (m, 1H).

Single-configuration Compound 191-2:

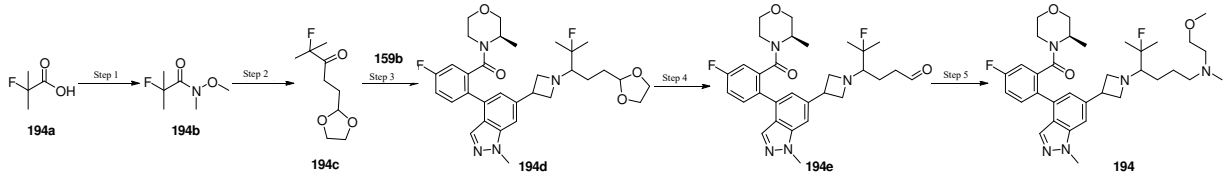
MS m/z (ESI):648.3 [M+1]

HPLC: retention time: 3.116 min.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.22 (m, 0.5H), 7.85 – 7.71 (m, 1H), 7.64 – 7.26 (m, 4H), 6.94 – 6.60 (m, 2H), 4.31 – 4.12 (m, 1H), 4.08 – 4.01 (m, 3H), 3.86 – 3.76 (m, 1H), 3.26 – 2.83 (m, 10H), 2.80 – 2.60 (m, 2H), 2.46 – 2.31 (m, 1H), 2.19 (s, 2H), 1.51 (s, 2H), 1.36 (s, 9H), 1.31 – 1.21 (m, 4H), 1.20 – 1.07 (m, 3H), 1.04 – 0.92 (m, 1H), 0.81 (s, 3H), 0.49 – 0.13 (m, 1H).

Example 194

{5-fluoro-4-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl}(2-methoxyethyl)methylamine **194**



Step 1

2-fluoro-*N*-methoxy-*N*,2-dimethylpropionamide **194b**

2-Fluoro-2-methylpropionic acid **194a** (10 g, 94.25 mmol) and triethylamine (36.40 g, 359.72 mmol) were dissolved in dichloromethane (200 mL), followed by the addition of EDCI (23.49 g, 122.53 mmol) and HOBt (16.56 g, 122.53 mmol), and the mixture was stirred at room temperature for 5.0 min, followed by the addition of N-methoxymethylamine (13.79 g, 141.38 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 12 hours. Water (300 mL) was added to the reaction mixture, which was then extracted with dichloromethane (100 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **194b** (7.1 g, 47.60 mmol, yield: 50.5%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.24 (s, 3H),1.64 (s, 3H), 1.58 (s, 3H).

Step 2

1-(1,3-dioxolan-2-yl)-4-fluoro-4-methylpentan-3-one **194c**

Under the protection of nitrogen, Mg(1.61 g, 66.29 mmol) was suspended in THF(20 mL), followed by the addition of I_2(50 mg, 197.00 μmol). 2-(2-Bromoethyl)-1,3-dioxolane (10 g, 55.24 mmol) was dissolved in tetrahydrofuran (80 mL), and placed in a dropping funnel. A bromide solution (about 8.0 mL) was dropwise added to the suspension of Mg, and the reaction mixture was heated to 50°C to initiate the reaction, followed by the slow dropwise addition of the residual bromide solution. After dropwise addition, the mixture as stirred at room temperature for 1 hour. At 0°C, the prepared alkyl magnesium bromide tetrahydrofuran solution was slowly dropwise added to the solution of Compound **194b** (3.6 g, 24.13 mmol) in THF(30 mL). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (100 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (70 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **194c** (500 mg, 2.63 mmol,

yield: 10.89%) as yellow liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (t, J = 4.2 Hz, 1H), 4.01 – 3.80 (m, 4H), 2.81 (dt, J = 3.0, 7.4 Hz, 2H), 1.99 (dt, J = 4.3, 7.3 Hz, 2H), 1.50 – 1.42 (m, 6H).

Step 3

6-{1-[1-(1,3-dioxolan-2-yl)-4-fluoro-4-methylpentan-3-yl]azacyclobutan-3-yl}-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1H-indazole **194d**

Compound **159b** (215 mg, 526.36 μmol) and Compound **194c** (120.14 mg, 631.63 μmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (143.48 mg, 1.05 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (99.23 mg, 1.58 mmol) and stirring at 50°C for 12 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **194d** (56 mg, 96.11 μmol, yield: 18.26%).
MS m/z (ESI): 583.5 [M+1]

Step 4

5-fluoro-4-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexanal **194e**

Compound **194d** (56 mg, 96.11 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with dichloromethane (20 mL), and then washed with a saturated aqueous sodium carbonate solution (20 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **194e** (50 mg, 92.83 μmol, yield: 96.59%) as yellow solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 539.3 [M+1]

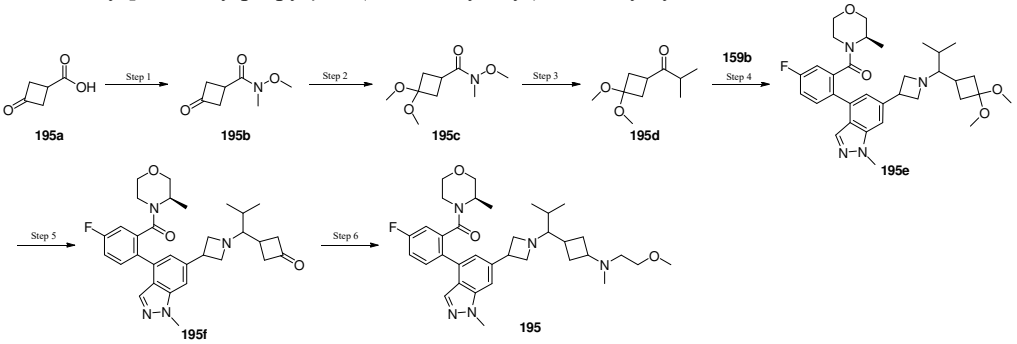
Step 5

{5-fluoro-4-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-5-methylhexyl}(2-methoxyethyl)methylamine **194**

The crude product of Compound **194e** (50 mg, 92.83 μmol) and 2-methoxy-*N*-methyl-ethylamine (9.93 mg, 111.39 μmol) were dissolved in methanol (1.0 mL), followed by the addition of acetic acid (5.57 mg, 92.83 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (17.50 mg, 278.49 μmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 0%-30%), to obtain the title Compound **194** (14.39 mg, 23.52 μmol, yield: 25.34%).
MS m/z (ESI):612.6 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1.18H), 8.01 – 7.82 (m, 1H), 7.80 – 7.58 (m, 1H), 7.57 – 7.16 (m, 4H), 4.49 – 3.77 (m, 7H), 3.72 – 3.31 (m, 10H), 3.31 – 2.96 (m, 5H), 2.95 – 2.63 (m, 5H), 2.56 – 2.32 (m, 1H), 1.99 – 1.83 (m, 2H), 1.53 – 1.33 (m, 8H), 1.27 – 1.04 (m, 2H), 0.55 – 0.09 (m, 1H).

Example 195

3-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-2-methylpropyl}-*N*-(2-methoxyethyl)-*N*-methylcyclobutan-1-amine **195**



Step 1

N-methoxy-*N*-methyl-3-oxocyclobutan-1-formamide **195b**

3-Oxocyclobutan-1-carboxylic acid **195a** (10 g, 87.64 mmol) and triethylamine (26.61 g, 262.93 mmol) were dissolved in dichloromethane (200 mL), followed by the addition of EDCI (20.16 g, 105.17 mmol) and HOBt(14.21 g, 105.17 mmol), and the mixture was stirred at room temperature for 5.0 min, followed by the addition of N-methoxymethylamine (10.26 g, 105.17 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 12 hours. Water (300 mL) was added to the reaction mixture, which was then extracted with dichloromethane (100 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **195b** (8.5 g, 54.08 mmol, yield: 61.71%) as yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.63 – 3.53 (m, 1H), 3.52 – 3.41 (m, 2H), 3.29 – 3.14 (m, 5H).

Step 2

N,3,3-trimethoxy-*N*-methylcyclobutan-1-formamide **195c**

Compound **195b** (4.0 g, 25.45 mmol) was dissolved in methanol (50 mL), followed by the addition of trimethyl orthoformate (5.40 g, 50.90 mmol) and 4-toluenesulfonic acid monohydrate (484.12 mg, 2.55 mmol), and the mixture was stirred at 50°C for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were dissolved with dichloromethane (60 mL), and washed with a saturated aqueous sodium bicarbonate solution (30 mL×3) and saturated brine (30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **195c** (4.5 g, 22.14 mmol, yield: 87%) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.20 – 3.14 (m, 10H), 2.39 (br d, J = 8.9 Hz, 4H).

Step 3

1-(3,3-dimethoxycyclobutyl)-2-methylpropan-1-one **195d**

Under the protection of nitrogen, Compound **195c** (2.0 g, 9.84 mmol) was dissolved in tetrahydrofuran (30 mL), and cooled to 0°C. An isopropylmagnesium chloride solution (2 M, 14.76 mL) was added dropwise to the reaction mixture, after which the reaction mixture was slowly warmed to room temperature and stirred for 2.0 hours . A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **195d** (1.1 g, 5.91 mmol, yield: 60.02%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.16 – 3.09 (m, 4H), 2.65 (td, J = 6.9, 13.9 Hz, 1H), 2.39 – 2.27 (m, 4H), 1.10 (d, J = 6.9 Hz, 6H).

Step 4

6-{1-[1-(3,3-dimethoxycyclobutyl)-2-methylpropyl]azacyclobutan-3-yl}-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-*1H*-indazole **195e**

Compound **159b** (200 mg, 489.63 μmol) and Compound **195d** (136.79 mg, 734.45 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (133.47 mg, 979.27 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (92.31 mg, 1.47 mmol) and stirring at 50°C for 10 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **195e** (250 mg, 431.99 μmol, yield: 88.23%).

MS m/z (ESI): 579.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.80 (m, 1H), 7.77 – 7.48 (m, 2H), 7.47 – 7.06 (m, 3H), 4.48 – 4.06 (m, 4H), 3.91 – 3.78 (m, 3H), 3.65 – 3.34 (m, 4H), 3.19 – 3.09 (m, 6H), 3.07 – 2.82 (m, 2H), 2.58 – 2.25 (m, 4H), 2.16 – 2.02 (m, 2H), 1.93 – 1.80 (m, 2H), 1.67 – 1.40 (m, 1H), 1.24 (d, J = 7.2 Hz, 1H), 1.07 (d, J = 6.8 Hz, 1H), 0.98 – 0.89 (m, 6H), 0.56 – 0.15 (m, 1H).

Step 5

3-{1-[3-(4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1H-indazol-6-yl)azacyclobutan-1-yl]-2-methylpropyl}cyclobutan-1-one **195f**

Compound **195e** (200 mg, 345.59 μmol) was dissolved in dichloromethane (6.0 mL), followed by the addition of trifluoroacetic acid (2.0 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hour. The reaction mixture was concentrated under a reduced pressure, diluted with a saturated aqueous sodium carbonate solution (20 mL), and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the title Compound **195f** (180 mg, 337.933 μmol, yield: 97.78%) as yellow solid.

MS m/z (ESI): 533.3 [M+1]

Step 6

3-{1-[3-(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-2-methylpropyl}-*N*-(2-methoxyethyl)-*N*-methylcyclobutan-1-amine **195**

Compound **195f** (90 mg, 168.97 μmol) and 2-methoxy-*N*-methyl-ethylamine (18.07 mg, 202.76 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (46.06 mg, 337.93 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (31.85 mg, 506.90 μmol), allowing for reacting at 50°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compound **195** (39.42 mg, 65.07 μmol, yield: 38.51%).

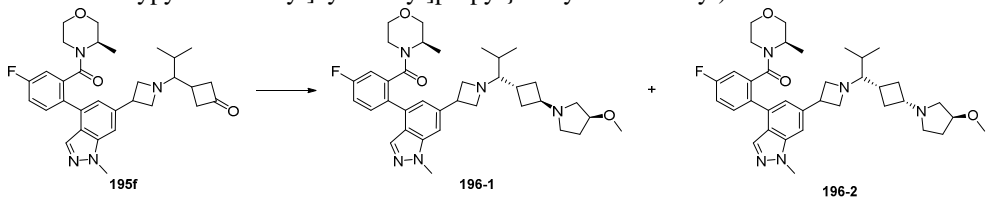
MS m/z (ESI):606.3 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.96 – 7.02 (m, 6H), 4.47 – 3.78 (m, 7H), 3.67 – 3.32 (m, 8H), 3.28 – 2.81 (m, 3H), 2.76 – 2.62 (m, 1H), 2.60 – 2.33 (m, 3H), 2.33 – 2.10 (m, 6H), 2.08 – 1.03 (m, 7H), 1.03 – 0.88 (m, 6H), 0.55 – 0.16 (m, 1H).

Examples 196-1 and 196-2

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-6-(1-{2-methyl-1-[(1*r*,3*r*)-3-[(3*S*)-3-methoxypyrrolidin-1-yl]cyclobutyl]propyl}azacyclobutan-3-yl)-1*H*-indazole **196-1**

4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-6-(1-{2-methyl-1-[(1*s*,3*s*)-3-[(3*S*)-3-methoxypyrrolidin-1-yl]cyclobutyl]propyl}azacyclobutan-3-yl)-1*H*-indazole **196-2**



Compound **195f** (180 mg, 337.93 μmol) and (3*S*)-3-methoxypyrrolidine (41.02 mg, 405.52 μmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (92.12 mg, 675.87 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (63.71 mg, 1.01 mmol), allowing for reacting at 50°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compounds **196-1** (4.7 mg, 7.61 μmol, yield: 2.25%) and **196-2** (11.86 mg, 19.20 μmol, yield: 5.68%).

Compound **196-1:**

MS m/z (ESI):618.3 [M+1]

HPLC: retention time: 0.755 min;

^{1}H NMR (400 MHz, CD_3OD) δ 7.96 – 7.04 (m, 6H), 4.63 – 3.67 (m, 8H), 3.66 – 3.32 (m, 4H), 3.29 – 2.19 (m, 15H), 2.16 – 1.53 (m, 6H), 1.52 – 1.02 (m, 3H), 1.00 – 0.87 (m, 5H), 0.54 – 0.16 (m, 1H).

Compound **196-2:**

MS m/z (ESI):618.4 [M+1]

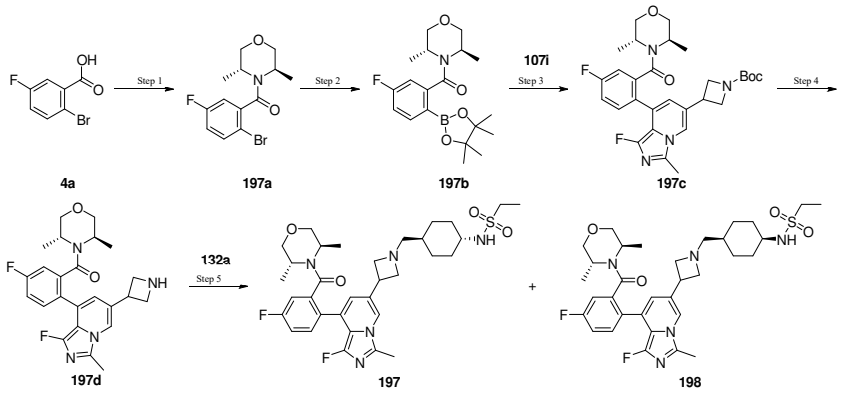
HPLC: retention time: 1.580 min.

^{1}H NMR (400 MHz, CD_3OD) δ 7.93 – 7.05 (m, 6H), 4.47 – 4.23 (m, 1H), 4.14 – 4.06 (m, 3H), 3.99 – 3.81 (m, 4H), 3.66 – 3.32 (m, 4H), 3.28 – 3.24 (m, 3H), 3.17 – 2.73 (m, 3H), 2.71 – 2.37 (m, 5H), 2.31 – 1.99 (m, 5H), 1.96 – 1.69 (m, 4H), 1.55 – 1.17 (m, 2H), 1.10 – 1.02 (m, 1H), 1.00 – 0.91 (m, 6H), 0.57 – 0.15 (m, 1H).

Examples 197 and 198

N-[(1*r*,4*r*)-4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **197**

N-[(1*s*,4*s*)-4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **198**



Step 1

(3*R*,5*R*)-4-(2-bromo-5-fluorobenzoyl)-3,5-dimethylmorpholine **197b**

2-Bromo-5-fluoro-benzoic acid **4a** (6.57 g, 29.98 mmol) was dissolved in dichloroethane (150 mL), followed by the addition of triethylamine (9.10 g, 89.93 mmol) and HATU (13.68 g, 35.97 mmol). The reaction mixture was stirred for 5 min, followed by the addition of (3*R*,5*R*)-3,5-dimethylmorpholine (5 g, 32.97 mmol, hydrochloride). The mixture was stirred at 50℃ for 12 hours. The mixture was washed with a saturated aqueous sodium carbonate solution (100 mL×2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain residues, i.e., crude products, which were then purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **197a** (8 g, 25.30 mmol, yield84.41%) as white solid.

MS m/z (ESI): 316.0 [M+1]

Step 2

(3*R*,5*R*)-4-[5-fluoro-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzoyl]-3,5-dimethylmorpholine **197b**

Compound **197a** (8 g, 25.30 mmol), potassium acetate (7.45 g, 75.91 mmol) and bis(pinacolato)diboron (16.06 g, 63.26 mmol) were dissolved in DMSO (100 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2.DCM (1.85 g, 2.53 mmol) was added, and the mixture was stirred at 110°C to allow for reacting for 5.0 hours. After the mixture was cooled to room temperature, 200 mL of water was added, and the mixture was extracted with ethyl acetate (100 ml × 3). The organic phases were combined, washed with water (100 ml×3), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain a crude product. The residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **197b** (5.45 g, 15.00 mmol, yield: 59.3%) as white solid.

MS m/z (ESI): 364.0 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (m, 1H), 7.26-7.20 (m, 2H), 3.78-3.63 (m, 4H), 3.48 – 3.44 (m, 2H), 1.26 (s, 12H), 1.16 (s, 3H), 1.11 (s, 3H)

Step 3

3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **197c**

Compound **107i** (2.16 g, 6.36 mmol), Compound **197b**(2.54 g, 6.99 mmol) and potassium phosphate (3.37 g, 15.89 mmol) were dissolved in dioxane (25 mL) and water (5.0 mL). Pd(dtbpf)Cl_2 (414.30 mg, 635.68 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **197c** (2.38 g, 4.40 mmol, yield: 69.3%).

MS m/z (ESI): 541.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_6$) δ 7.50 – 7.35 (m, 2H), 7.25 – 7.17 (m, 2H), 6.54 (br s, 1H), 4.29 (br t, J = 8.6 Hz, 2H), 4.06 – 3.57 (m, 6H), 3.49 – 3.11 (m, 2H), 2.99 – 2.74 (m, 1H), 2.63 (s, 3H), 1.46 (s, 9H), 1.18 – 0.95 (m, 6H).

Step 4

(3*R*,5R)-4-{2-[6-(azacyclobutan-3-yl)-1-fluoro3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3,5-dimethylmorpholine **197d**

Compound **197c** (1 g, 1.85 mmol) was dissolved in methane dioxide (15.0 mL), followed by the addition of trifluoroacetic acid (5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and residues were dissolved by adding dichloromethane (10.0 mL), regulated to PH = 11.0 with a 10% aqueous sodium hydroxide solution, and extracted

with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **197d** (870 mg, 1.98 mmol, yield: 106.8%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 441.1 [M+1]

Step 5

N-[(1*r*,4*r*)-4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **197**

N-[(1*s*,4*s*)-4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}cyclohexyl]ethan-1-sulfonamide **198**

The crude product of Compound **197d** (870 mg, 1.98 mmol) and *N*-[(1*r*,4*r*)-4-formylcyclohexyl]ethan-1-sulfonamide **132a**(476.45 mg, 2.17 mmol) were dissolved in methanol (15.0 mL). Acetic acid (142.33 mg, 2.37 mmol) was added, and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (372.36 mg, 5.93 mmol) was added, and the reaction mixture was stirred at room temperature for 2.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%), and then further separated by the preparative SFC(preparative column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: CO_2-EtOH(0.1% ammonia water); elution gradient: 30%), to obtain the title Compounds **197** (339.71 mg, 527.68 μmol, yield: 26.72%) and **198** (73.48 mg, 114.14 μmol, yield: 5.78%).

Compound 197:

MS m/z (ESI): 644.2[M+1]

SFC: retention time: 1.773 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.57 – 7.30 (m, 3H), 6.97 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 3.82 – 3.33 (m, 6H), 3.28 – 2.90 (m, 7H), 2.78 – 2.52 (m, 4H), 2.23 (d, J = 6.8 Hz, 2H), 1.89 – 1.67 (m, 4H), 1.27 – 0.78 (m, 14H).

Compound 198:

MS m/z (ESI): 644.2[M+1]

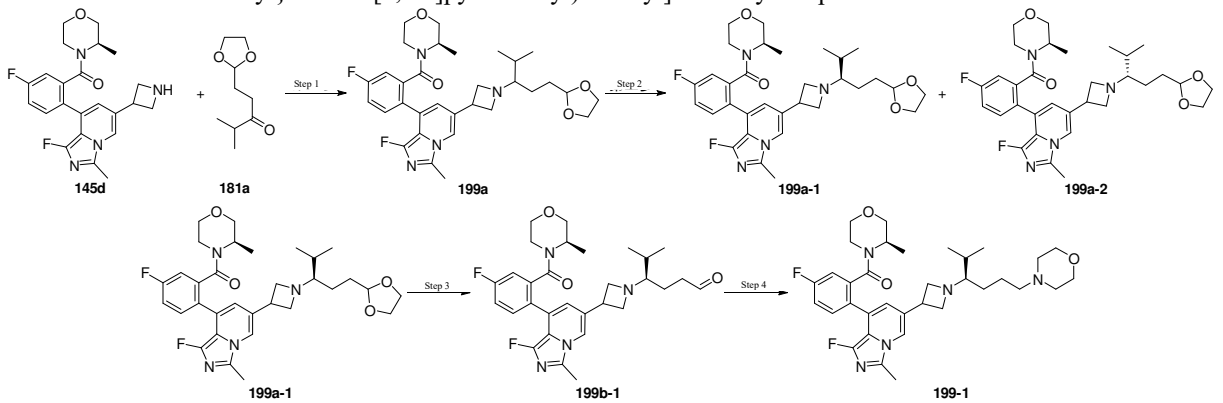
SFC: retention time: 1.584 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.

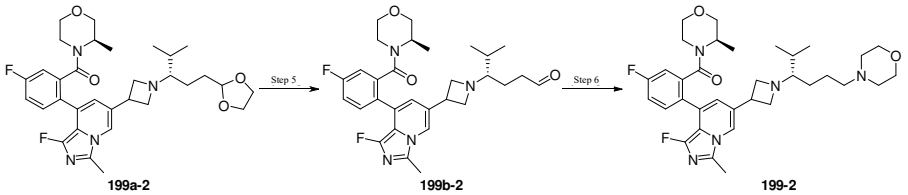
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.60 – 7.28 (m, 3H), 7.08 – 6.77 (m, 1H), 6.70 – 6.46 (m, 1H), 3.86 – 3.38 (m, 6H), 3.28 – 2.82 (m, 7H), 2.76 – 2.53 (m, 4H), 2.37 – 2.24 (m, 2H), 1.62 – 1.29 (m, 9H), 1.26 – 0.73 (m, 9H).

Examples 199-1 and 199-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-2-methyl-6-(morpholin-4-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **199-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-2-methyl-6-(morpholin-4-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **199-2**





Step 1

(3*R*)-4-[2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **199a**

Compound **145d** (422 mg, 989.55 μmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (187.46 mg, 1.09 mmol) were dissolved in methanol (20 mL), followed by the addition of $ZnCl_2$ (404.61 mg, 2.97 mmol), and the mixture was stirred at 60°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (186.55 mg, 2.97 mmol) and stirring at 60°C for 4.0 hour. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then stirred for 30 min and then diluted with water (50 mL). The mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the crude product of title Compound **199a** (500 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 583.6 [M+1]

Step 2

(3*R*)-4-[2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **199a-1**

(3*R*)-4-[2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **199a-2**

The crude product of Compound **199a** (500 mg) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 45%), to obtain the crude products of title Compounds **199a-1** (151 mg, 259.15 μmol, yield: 26.19%) and **199a-2** (151 mg, 259.15 μmol, yield: 26.19%).

Single-configuration Compound 199a-1:

MS m/z (ESI):583.3 [M+1]

Chiral HPLC analysis: retention time: 1.845 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 199a-2:

MS m/z (ESI):583.3 [M+1]

Chiral HPLC analysis: retention time: 1.462 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexanal **199b-1**

Compound **199a-1** (151.00 mg, 259.15 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 12 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **199b-1** (116 mg, 215.36 μmol,yield: 83.1%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 199b-1:

MS m/z (ESI): 539.2 [M+1]

Step 4

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-2-methyl-6-(morpholin-4-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **199-1**

The crude product of Compound **199b-1** (45 mg, 83.55 μmol) and morpholine (8.73 mg, 100.25 μmol) were dissolved in methanol (3 mL). Sodium cyanoborohydride (10.50 mg, 167.09 μmol) and triethylamine (25.36 mg, 250.64 μmol) were added, allowing for reacting at 30°C for 2.0 hours under the protection of nitrogen. Sodium cyanoborohydride (5.25 mg, 83.55 μmol) was supplemented, and the mixture was further stirred for 0.5 hours. Water was added to the

reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-63%). The title Compound **199-1** (0.85 mg, 1.39 μmol, yield: 1.67%) was obtained.

Single-configuration Compound 199-1:

MS m/z (ESI):610.2 [M+1]

Chiral SFC: retention time: 1.177 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.43 (m, 2H), 7.26 – 7.10 (m, 2H), 6.85 – 6.61 (m, 1H), 4.71 – 3.83 (m, 4H), 3.81 – 3.55 (m, 8H), 3.42 – 3.21 (m, 3H), 3.20 – 3.04 (m, 1H), 3.03 – 2.89 (m, 1H), 2.82 – 2.70 (m, 1H), 2.63 (s, 3H), 2.54 – 2.29 (m, 8H), 1.37 – 1.10 (m, 4H), 0.98 (s, 6H), 0.86 – 0.73 (m, 1H).

Step 5

(4*S*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexanal **199b-2**

Compound **199a-2** (151.00 mg, 259.15 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 12 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **199b-2** (96 mg, 178.23 μmol, yield: 68.78%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 199b-2:

MS m/z (ESI): 539.2 [M+1]

Step 6

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-2-methyl-6-(morpholin-4-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **199-2**

The crude product of Compound **199b-2** (32 mg, 59.41 μmol) and morpholine (5.69 mg, 65.35 μmol) were dissolved in methanol (3.0 mL), and stirred at 30°C for 0.5 hours. Sodium cyanoborohydride (11.20 mg, 178.23 μmol) was added, allowing for reacting at 30°C for 11.0 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) were added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 30%-60%). The title Compound **199-2** (5.94 mg, 9.74 μmol, yield: 16.40%) was obtained as yellow solid.

Single-configuration Compound 199-2:

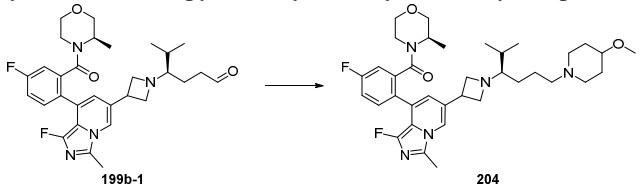
MS m/z (ESI):610.5 [M+1]

Chiral SFC: retention time: 1.172 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.30 (m, 2H), 7.17 – 6.98 (m, 2H), 6.75 – 6.47 (m, 1H), 5.29 – 4.02 (m,1H), 3.75 – 3.66 (m, 1H), 3.63 (br s, 3H), 3.56 – 3.45 (m, 2H), 3.39 – 3.20 (m, 1H), 3.16 – 3.05 (m, 2H), 3.01 – 2.62 (m, 2H), 2.53 (s, 3H), 2.37 (br s, 4H), 2.29 – 2.19 (m, 2H), 2.14 – 1.87 (m, 2H), 1.81 – 1.63 (m, 4H), 1.54 – 1.44 (m, 2H), 1.31 – 1.18(m, 3H), 1.12 – 1.00 (m, 1H), 0.90 – 0.79 (m, 6H), 0.75 – 0.03 (m, 1H).

Example 204

(3*R*)-4-[5-fluoro-2-(1-fluoro-6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **204**



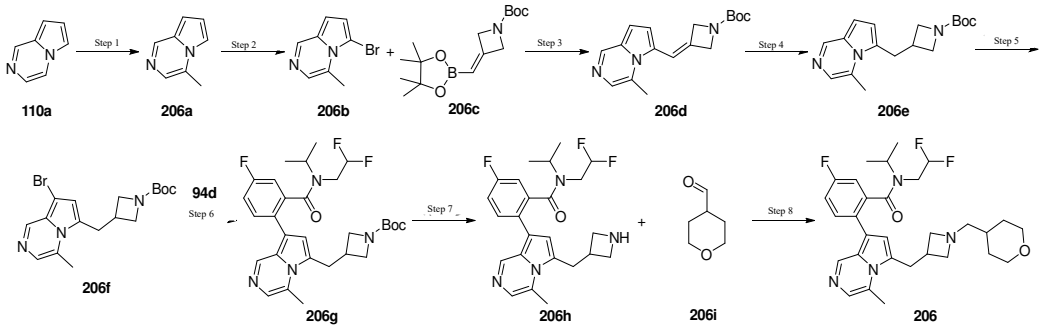
199b-1 204

The crude product of Compound **199b-1** (100 mg, 185.66 μmol) and 4-methoxypiperidine (23.52 mg, 204.22 μmol) were dissolved in methanol (1.5 mL), followed by the addition of acetic acid (16.72 mg, 278.49 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (35.00 mg, 556.97 μmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column

chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 43%-73%), to obtain the title product **204** (42.8 mg, 67.11 μmol, yield: 36.14%) as yellow solid.
MS m/z (ESI):638.4 [M+1]
Chiral SFC: retention time: 1.164 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.78 (m, 1H), 7.65 – 7.21 (m, 3H), 6.90 – 6.39 (m, 1H), 4.41 – 3.88 (m, 1H), 3.76 – 3.44 (m, 5H), 3.20 (s, 3H), 3.12 (s, 3H), 2.75 – 2.61 (m, 2H), 2.55 (s, 3H), 2.35 – 2.18 (m, 2H), 2.11 – 1.99 (m, 2H), 1.83 – 1.67 (m, 3H), 1.51 – 1.34 (m, 4H), 1.29 – 1.03 (m, 7H), 0.89 – 0.70 (m, 8H).

Example 206

N-(2,2-difluoroethyl)-5-fluoro-2-[4-methyl-6-({1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **206**



Step 1

4-methylpyrrolo[1,2-*a*]pyrazine **206a**

Pyrrolo[1,2-a]pyrazine **110a** (1.0 g, 8.46 mmol) was dissolved in THF (40 mL), and cooled to -75 °C, followed by the slow dropwise addition of the THF solution (2 M, 9.50 mL) of LDA. The reaction mixture was stirred at -75 °C for 0.5 hours, followed by the addition of iodomethane (3.12 g, 22.01 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 2.0 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **206a** (2.2 g, 16.65 mmol, yield: 98.33%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 133.2[M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.40 (s, 1H), 7.35 – 7.31 (m, 1H), 6.96 (dd, J = 2.6, 4.0 Hz, 1H), 6.86 (dd, J = 1.0, 4.1 Hz, 1H), 2.50 (s, 3H).

Step 2

6-bromo-4-methylpyrrolo[1,2-*a*]pyrazine **206b**

Compound **206a** (1.2 g, 9.08 mmol) was dissolved in trichloromethane (25 mL), and cooled to -10 °C, followed by the addition of NBS(1.54 g, 8.63 mmol). The reaction mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (40 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **206b** (750 mg, 3.55 mmol, yield: 39.14%).

MS m/z (ESI): 213.0[M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.40 (s, 1H), 7.35 – 7.31 (m, 1H), 6.96 (dd, J = 2.6, 4.0 Hz, 1H), 6.86 (dd, J = 1.0, 4.1 Hz, 1H), 2.50 (s, 3H).

Step 3

3-({4-methylpyrrolo[1,2-a]pyrazin-6-yl}methylene)azacyclobutan-1-tert-butyl carboxylate **206d**

Compound **206b** (100 mg, 473.80 μmol), 3-[(tetramethyl-1,3,2-dioxaboran-2-yl)methylene]azacyclobutan-1-tert-butyl carboxylate **206c** (205.12 mg, 521.18 μmol) and sodium carbonate (150.65 mg, 1.42 mmol) were dissolved in dioxane (6 mL) and water (1 mL). $Pd(dtbpf)Cl_2$ (30.88 mg, 47.38 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an

elution system, to obtain the title Compound **206d** (123 mg, 410.87 μmol, yield: 86.72%).
MS m/z (ESI): 299.9 [M+1]

Step 4

3-({4-methylpyrrolo[1,2-a]pyrazin-6-yl}methyl)azacyclobutan-1-tert-butyl carboxylate **206e**

Compound **206d** (488 mg, 1.63 mmol) was dissolved in methanol (10 mL), followed by the addition of 10% Pd/C (395.97 mg, 326.02 μmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (15 psi), and the mixture was stirred at 50°C for 12.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **206e** (418 mg, 1.39 mmol, yield: 85.08%).
MS m/z (ESI): 301.9 [M+1]

Step 5

3-({8-bromo-4methylpyrrolo[1,2-a]pyrazin-6-yl}methyl)azacyclobutan-1-tert-butyl carboxylate **206f**

Compound **206e** (212 mg, 703.43 μmol) was dissolved in trichloromethane (5.0 mL), and cooled to -10°C, followed by the addition of NBS (118.94 mg, 668.25 μmol), and the mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (40 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **206f** (170 mg, 447.04 μmol, yield: 63.55%).
MS m/z (ESI): 382.0 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.16 (s, 1H), 6.71 (s, 1H), 4.16 – 4.08 (m, 2H), 3.71 – 3.65 (m, 2H), 3.62 (d, J = 8.0 Hz, 2H), 3.08 – 2.98 (m, 1H), 2.80 (s, 3H), 1.43 (s, 9H).

Step 6

3-[(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **206g**

Compound **206f** (200 mg, 525.93 μmol) and Compound **94d** (292.84 mg, 788.90 μmol) were dissolved in dioxane (8 mL) and water (1.0 mL). Potassium phosphate (247.98 mg, 1.58 mmol) and Pd(dtbpf)Cl_2 (34.28 mg, 52.59 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **206g** (244 mg, 448.03 μmol, yield: 85.19%).
MS m/z (ESI): 545.2 [M+1]

Step 7

2-{6-[(azacyclobutan-3-yl)methyl]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-(isopropyl)benzamide **206h**

Compound **206g** (80 mg, 146.89 μmol) was dissolved in dichloromethane (5.47 mL), followed by the addition of trifluoroacetic acid (789.33 mg, 6.92 mmol, 533.33 μL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **206h** (65.3 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 445.1 [M+1]

Step 8

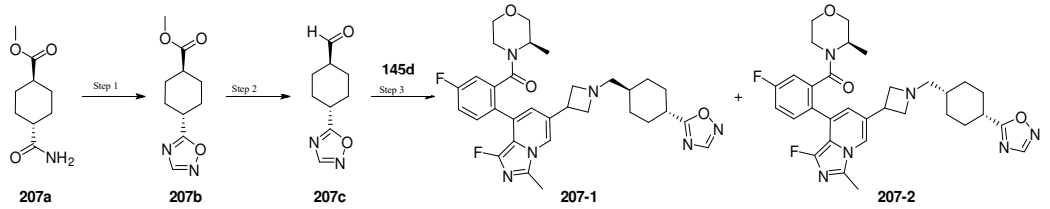
N-(2,2-difluoroethyl)-5-fluoro-2-[4-methyl-6-({1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **206**

The crude product of Compound **206h** (65.3 mg), oxacyclohexan-4-formaldehyde **206i** (21.80 mg, 190.95 μmol) and triethylamine (44.59 mg, 440.66 μmol) were dissolved in methanol (10 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (18.46 mg, 293.77 μmol) was added, and the mixture was stirred at 50°C for 2.0 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **206** (13.68 mg, 25.21 μmol, yield: 17.16%) as yellow solid.
MS m/z (ESI): 543.2 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 7.55 (dd, J = 5.6, 8.8 Hz, 1H), 7.32 (dt, J = 2.8, 8.8 Hz, 1H), 7.26 – 7.13 (m, 2H), 6.67 (s, 1H), 6.13 – 5.75 (m, 1H), 3.96 – 3.87 (m, 2H), 3.65 – 3.61 (m, 3H), 3.59 – 3.51 (m, 1H), 3.42 – 3.35 (m, 2H), 3.13 – 3.04 (m, 2H), 3.02 – 2.91 (m, 1H), 2.83 (s, 3H), 2.47 (d, J = 6.4 Hz, 2H), 1.70 – 1.59 (m, 3H), 1.39 – 1.19 (m, 6H), 0.95 (d, J = 6.4 Hz, 3H), 0.33 (d, J = 6.8 Hz, 2H).

Examples 207-1 and 207-2

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1,2,4-oxadiazol-5-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **207-1**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1,2,4-oxadiazol-5-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a] pyridin-8yl]benzoyl}-3-methylmorpholine **207-2**



Step 1

(1r,4r)-4-(1,2,4-oxadiazol-5-yl)cyclohexan-1-methyl carboxylate **207b**

(1*r*,4*r*)-4-aminoformylcyclohexan-1-methyl carboxylate **207a** (1 g, 5.40 mmol) was dissolved in 1,1-dimethoxy-*N,N*-dimethyl-methylamine (8.97 g, 75.28 mmol, 10 mL). The reaction mixture was stirred at 100°C for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, and the obtained solid was dissolved in ethanol (30 mL), followed by the addition of hydroxylamine in hydrochloride (750.36 mg, 10.80 mmol). The mixture was stirred at 80°C for 12 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **207b** (750 mg, 3.57 mmol, yield: 66.08%) as white solid.

MS m/z (ESI): 211.1 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 3.70 (s, 3H), 3.08 – 2.93 (m, 1H), 2.44 – 2.35 (m, 1H), 2.30 – 2.22 (m, 2H), 2.20 – 2.11 (m, 2H), 1.73 – 1.59 (m, 4H).

Step 2

(1*r*,4*r*)-4-(1,2,4-oxadiazol-5-yl)cyclohexan-1-formaldehyde **207c**

Compound **207b** (740 mg, 3.52 mmol) was dissolved in DCM(10 mL). Under a nitrogen atmosphere, the mixture was cooled to -75°C, followed by the slow dropwise addition of DIBAL-H (1 M, 3.87 mL), and the mixture was stirred at -75°C to allow for reacting for 2.0 hours. Sodium sulfate decahydrate was added to quench the reaction, the reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure to obtain a crude product. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **207c** (180 mg, 998.87 μmol, yield: 28.38%) as colorless oil.

MS m/z (ESI): 181.1 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.34 (s, 1H), 2.98 (tt, J = 3.6, 11.9 Hz, 1H), 2.35 – 2.26 (m, 3H), 2.22 – 2.15 (m, 2H), 1.77 – 1.67 (m, 2H), 1.53 – 1.38 (m, 2H).

Step 3

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1,2,4-oxadiazol-5-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **207-1**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1,2,4-oxadiazol-5-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **207-2**

The crude product of Compound **145d** (95 mg, 180.41 μmol) and Compound **207c** (48.17 mg, 267.32 μmol) were dissolved in methanol (2.0 mL). Acetic acid (13.38 mg, 222.77 μmol) was added, and the mixture was stirred for 1.0 hour. Sodium cyanoborohydride (42.00 mg, 668.30 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compounds **207-1** (18.67 mg, 31.61 μmol, yield: 14.19%) and **207-2** (17.24 mg, 29.19 μmol, yield: 13.10%).

Compound 207-1:

MS m/z (ESI): 591.2[M+1]

SFC: retention time: 0.850 min; Chiralpak AS-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 8.63 – 8.40 (m, 1H), 7.89 – 7.76 (m, 1H), 7.66 – 7.50 (m, 1H), 7.38 – 7.16 (m, 2H), 6.86 – 6.60 (m, 1H), 4.61 – 4.20 (m, 1H), 4.14 – 3.48 (m, 6H), 3.21 – 2.66 (m, 4H), 2.64 – 2.48 (m, 5H), 2.21 – 1.82 (m, 5H), 1.77 – 0.94 (m, 8H), 0.83 – 0.62 (m, 1H).

Compound 207-2:

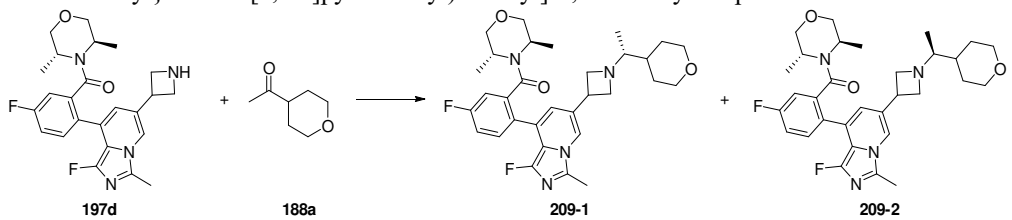
MS m/z (ESI): 591.3[M+1]

SFC: retention time: 2.171 min; Chiralpak OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 8.60 – 8.18 (m, 1H), 8.04 – 7.87 (m, 1H), 7.80 – 7.44 (m, 1H), 7.43 – 7.08 (m, 2H), 7.03 – 6.42 (m, 1H), 4.52 – 4.15 (m, 5H), 3.64 – 3.55 (m, 1H), 3.43 – 3.39 (m, 1H), 3.23 – 3.16 (m, 2H), 3.04 – 2.95 (m, 1H), 2.71 – 2.55 (m, 3H), 2.21 – 2.10 (m, 2H), 1.98 – 1.78 (m, 5H), 1.70 – 1.39 (m, 5H), 1.30 – 1.05 (m, 4H), 0.82 – 0.64 (m, 1H).

Examples 209-1 and 209-2

(3*R*,5*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*)-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3,5-dimethylmorpholine **209-1**

(3*R*,5*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*S*)-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3,5-dimethylmorpholine **209-2**



Compound **197d** (159 mg, 360.97 μmol) and Compound **188a** (50.89 mg, 397.06 μmol) were dissolved in methanol (2.0 mL). Zinc chloride (98.40 mg, 721.93 μmol) was added, and the mixture was stirred at 50°C for 1.0 hour. After cooling, sodium cyanoborohydride (68.05 mg, 1.08 mmol) was added, and the mixture was further stirred at 50°C for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), and the resulting mixture was separated by the chiral preparative HPLC (preparative column: Daicel ChiralPak IG (250 * 30 mm, 10 um); mobile phase: n-hexan-EtOH(0.1% isopropylamine); elution gradient: 20%), to obtain the title Compounds **209-1** (16.80 mg, 30.40 μmol, yield: 8.42%) and **209-2** (27.6 mg, 49.94 μmol, yield: 13.84%).

Compound 209-1:

MS m/z (ESI): 553.1[M+1]
Chiral HPLC: retention time: 2.590 min; Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-[EtOH+ACN(0.05%DEA)]; elution gradient: 20%;
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.54 – 7.47 (m, 1H), 7.45 – 7.35 (m, 2H), 6.62 (s, 1H), 3.92 – 3.41 (m, 8H), 3.28 – 3.03 (m, 6H), 2.69 – 2.52 (m, 4H), 2.16 (s, 1H), 1.61 – 1.44 (m, 2H), 1.35 – 1.28 (m, 2H), 1.26 – 1.16 (m, 2H), 0.85 (s, 5H), 0.78 – 0.74 (m, 3H).

Compound 209-2:

MS m/z (ESI): 553.2[M+1]
Chiral HPLC: retention time: 2.583 min; Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-[EtOH+ACN(0.05%DEA)]; elution gradient: 20%;
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.54 – 7.47 (m, 1H), 7.45 – 7.35 (m, 2H), 6.57 (s, 1H), 3.93 – 3.34 (m, 8H), 3.29 – 3.01 (m, 6H), 2.75 – 2.53 (m, 4H), 2.20 – 2.12 (m, 1H), 1.62 – 1.43 (m, 2H), 1.37 – 1.13 (m, 4H), 1.06 – 0.74 (m, 8H).

Example 211

4-[(4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-yl)methyl]oxacyclohexan-4-ol **211**

Step 1

4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-tert-butyl carboxylate **211a**

Compound **197d** (1.63 g, 3.70 mmol), 4-formylpiperidin-1-tert-butyl formate **171a** (1.03 g, 4.81 mmol) and acetic acid (222.22 mg, 3.70 mmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (697.63 mg, 11.10 mmol) was added, and the reaction mixture was stirred at room

temperature for 12 hour. The reaction mixture was concentrated under a reduced pressure, and the residues was added to water (20 mL), and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **211a** (2.3 g, 3.61 mmol, yield: 97.46%) as yellow oil.
MS m/z (ESI): 638.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.85 (m, 1H), 7.55 – 7.47 (m, 1H), 7.46 – 7.36 (m, 2H), 6.61 (br s, 1H), 4.10 (br d, J = 4.4 Hz, 2H), 3.90 (br d, J = 12.6 Hz, 2H), 3.67 – 3.54 (m, 4H), 3.02 (br d, J = 6.8 Hz, 8H), 2.55 (s, 3H), 2.37 – 2.30 (m, 1H), 1.69 – 1.61 (m, 2H), 1.38 (s, 12H), 1.05 – 0.91 (m, 6H).

Step 2

(3*R*,5*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(piperidin-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3,5-dimethylmorpholine **211b**

Compound **211a** (160 mg, 250.88 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **211b** (130 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 538.3 [M+1]

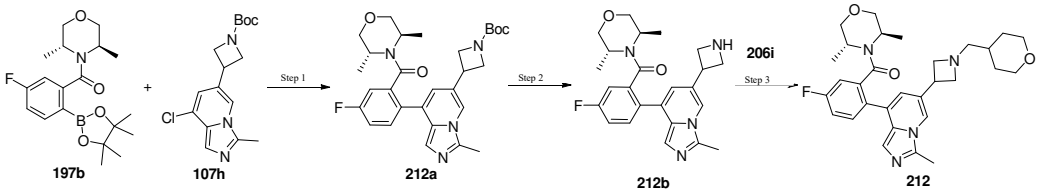
Step 3

4-[(4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-yl)methyl]oxacyclohexan-4-ol **211**

Compound **211b** (78.20 mg, 120 μmol, trifluoroacetate), triethylamine (60.71 mg, 600.00 μmol) and 1,6-dioxaspiro[2.5]octane (27.39 mg, 240.00 μmol) were dissolved in isopropanol (1.0 mL), and stirred at 60°C for 12 hours and the reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title Compound **211** (5.09 mg, 7.81 μmol, yield: 6.51 %) as yellow solid.
MS m/z (ESI): 652.5 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (s, 1H), 7.59 – 7.47 (m, 1H), 7.41 – 7.27 (m, 2H), 6.65 (s, 1H), 3.92 – 3.65 (m, 9H), 3.46 – 3.33 (m, 1H), 3.30 – 3.09 (m, 4H), 2.99 – 2.78 (m, 3H), 2.60 (s, 3H), 2.49 – 2.40 (m, 2H), 2.31 (s, 2H), 2.27 – 2.18 (m, 2H), 1.75 – 1.57 (m, 4H), 1.53 – 0.89 (m, 11H).

Example 212

(3*R*,5*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3,5-dimethylmorpholine **212**



Step 1

3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **212a**

Compound **107h** (300 mg, 932.25 μmol), Compound **197b**(372.48 mg, 1.03 mmol) and potassium phosphate (495 mg, 2.33 mmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). Pd(dtbpf)Cl_2 (61 mg, 93.59 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **212a** (400 mg, 765.39 μmol, yield: 82.1%).
MS m/z (ESI): 523.2 [M+1]

Step 2

(3*R*,5*R*)-4-{2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3,5-dimethylmorpholine **212b**

Compound **212a** (110 mg, 210.48 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **212b** (110 mg). The crude product was directly used in the next step of reaction without

purification.
MS m/z (ESI): 423.1 [M+1]

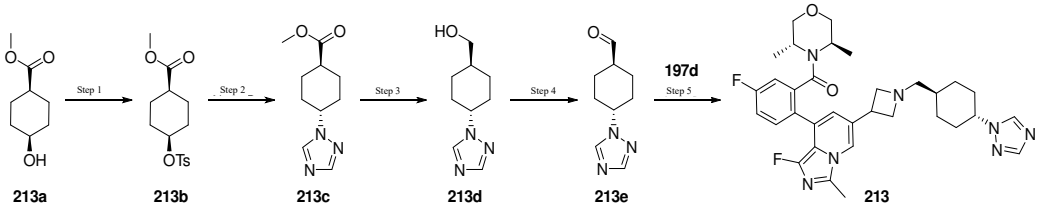
Step 3

(3*R*,5*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3,5-dimethylmorpholine **212**

The crude product of Compound **212b** (110 mg) and Compound **206i** (28.76 mg, 252.00 μmol) were dissolved in methanol (2.0 mL), followed by the addition of triethylamine (25.50 mg, 252.00 μmol), and the mixture was stirred at 25°C for 0.5 hours. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (39.59 mg, 630.00 μmol) and stirring at 25°C for 11.0 hour. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 0%-26%), to obtain the title Compound **212** (29.98 mg, 57.58 μmol, yield: 27.42 %).
MS m/z (ESI): 521.3 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1.31H), 8.11 (s, 1H), 7.64 (s, 1H), 7.45 – 7.32 (m, 2H), 7.10 (s, 1H), 6.84 (s, 1H), 4.52 – 4.36 (m, 2H), 4.27 – 4.10 (m, 3H), 4.01 – 3.90 (m, 2H), 3.85 – 3.64 (m, 2H), 3.48 – 3.36 (m, 3H), 3.27 – 3.11 (m, 3H), 2.71 (s, 5H), 2.02 – 1.88 (m, 1H), 1.74 – 1.62 (m, 2H), 1.45 – 1.28 (m, 2H), 1.24 – 0.58 (m, 6H).

Example 213

(3*R*,5*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3,5-dimethylmorpholine **213**



Step 1

(1*s*,4*s*)-4-[(4-methylphenylsulfonyl)oxy]cyclohexan-1-methyl carboxylate **213b**

(1*s*,4*s*)-4-hydroxylcyclohexan-1-methyl carboxylate **213a** (5 g, 31.61 mmol) was dissolved in DCM(70 mL), followed by the addition of DMAP (386.14 mg, 3.16 mmol) and triethylamine (9.59 g, 94.82 mmol). The reaction mixture was cooled to 0°C, followed by adding 4-toluensulfonyl chloride (7.23 g, 37.93 mmol). The reaction mixture was stirred at 25°C for 12.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **213b** (6.0 g, 19.21 mmol, yield60.77%) as yellow solid.
MS m/z (ESI): 330.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.74 (m, 2H), 7.50 – 7.41 (m, 2H), 4.71 – 4.60 (m, 1H), 3.62 – 3.55 (m, 3H), 2.43 – 2.35 (m, 4H), 1.67 – 1.56 (m, 8H).

Step 2

(1*r*,4*r*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexan-1-methyl carboxylate **213c**

1*H*-1,2,4-triazole (1 g, 14.48 mmol) was dissolved in acetonitrile (40 mL), followed by the addition of Compound **213b** (3.62 g, 11.58 mmol), cesium carbonate (9.44 g, 28.96 mmol) and TBAI(534.81 mg, 1.45 mmol). The reaction mixture was heated to 85°C and stirred for 6.0 hours. The reaction mixture was filtered under a reduced pressure, and washed with ethyl acetate (100 mL), and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **213c** (500 mg, 2.39 mmol, yield16.5%) as white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.99 – 7.89 (m, 1H), 4.34 – 4.23 (m, 1H), 3.62 – 3.60 (m, 3H), 2.45 – 2.36 (m, 1H), 2.11 – 2.00 (m, 4H), 1.83 – 1.73 (m, 2H), 1.58 – 1.48 (m, 2H).

Step 3

[(1*r*,4*r*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methanol **213d**

Compound **213c** (500 mg, 2.39 mmol) was dissolved in DCM(5 mL). Under a nitrogen atmosphere, the mixture was cooled to 0°C, followed by the slow dropwise addition of DIBAL-H (1 M, 4.78 mL), and the mixture was warmed to room temperature and stirred to allow for reacting for 5.0 hours. DIBAL-H (1 M, 2.0 mL) was supplemented, and the mixture was stirred at room temperature to allow for reacting for 12 hours . The reaction mixture was quenched by adding sodium sulfate decahydrate and filtered, and the filtrate was concentrated under a reduced pressure, to

obtain the crude product of title Compound **213d** (350 mg, 1.93 mmol, yield: 80.82%) as white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.96 – 7.89 (m, 1H), 4.50 – 4.45 (m, 1H), 4.27 – 4.13 (m, 1H), 3.28 – 3.22 (m, 2H), 2.09 – 2.02 (m, 2H), 1.89 – 1.81 (m, 2H), 1.77 – 1.64 (m, 2H), 1.50 – 1.35 (m, 1H), 1.14 – 1.01 (m, 2H).

Step 4

(1*r*,4*r*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexan-1-formaldehyde **213e**

Compound **213d** (150 mg, 827.66 μmol) was dissolved in DMSO(4 mL). Under a nitrogen atmosphere, the mixture was cooled to 0°C, and a Burgess reagent (256.41 mg, 1.08 mmol) was added slowly. The reaction mixture was stirred at room temperature to allow for reacting for 12 hour. In an ice water bath, water (5 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **213e** (50 mg, 278.99 μmol, yield: 33.71%) as colorless oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.52 – 8.50 (m, 1H), 7.94 – 7.93 (m, 1H), 4.27 – 4.23 (m, 1H), 2.09 – 2.07 (m, 2H), 1.80 – 1.77 (m, 2H), 1.56 – 1.49 (m, 2H), 1.40 – 1.36 (m, 1H), 1.29 – 1.18 (m, 2H).

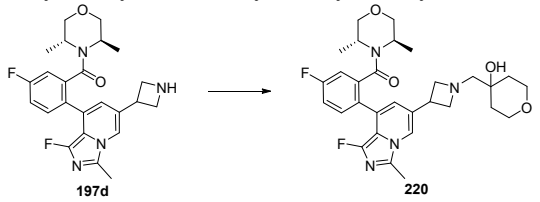
Step 5

(3*R*,5*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3,5-dimethylmorpholine **213**

Compound **197d** (40 mg, 90.81 μmol) and Compound **213e** (50.00 mg, 278.99 μmol) were dissolved in methanol (2.0 mL). Acetic acid (5.45 mg, 90.81 μmol) was added, and the mixture was stirred for 1.0 hour. Sodium cyanoborohydride (17.12 mg, 272.43 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 27%-57%), to obtain the title Compound **213** (8.78 mg, 14.54 μmol, yield: 16.02%).
MS m/z (ESI): 604.2[M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.98 – 7.94 (m, 1H), 7.87 – 7.81 (m, 1H), 7.56 – 7.49 (m, 1H), 7.37 – 7.31 (m, 2H), 6.74 – 6.60 (m, 1H), 4.61 – 4.59 (m, 1H), 4.33 – 4.24 (m, 1H), 3.93 – 3.64 (m, 6H), 2.96 – 2.78 (m, 1H), 2.62 – 2.60 (m, 3H), 2.54 – 2.48 (m, 2H), 2.20 – 2.12 (m, 2H), 2.06 – 1.76 (m, 5H), 1.59 – 1.47 (m, 1H), 1.41 – 0.73 (m, 10H).

Example 220

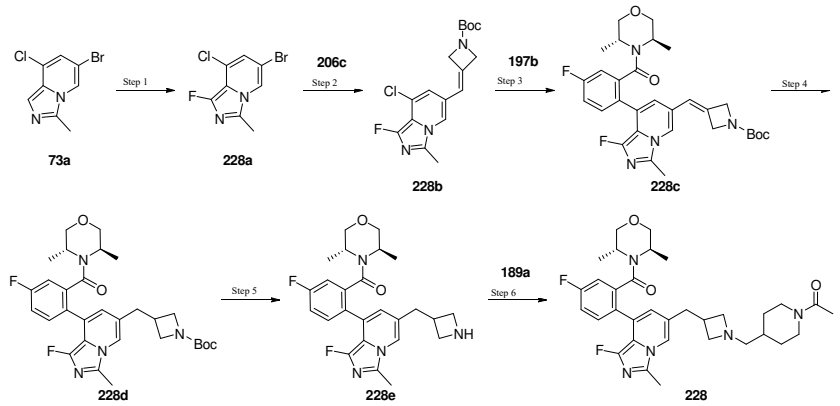
4-{[3-(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}oxacyclohexan-4-ol **220**



Compound **197d** (88.72 mg, 160 μmol, trifluoroacetate), triethylamine (80.95 mg, 800.00 μmol) and 1,6-dioxaspiro[2.5]octane (36.53 mg, 320.00 μmol) were dissolved in isopropanol (1.0 mL), and stirred at 60°C for 12 hours and the reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:23%-53%), to obtain the title Compound **220** (31.11 mg, 56.09 μmol, yield: 35.06%) as yellow solid.
MS m/z (ESI): 555.2 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.58 – 7.33 (m, 3H), 6.60 (s, 1H), 4.08 (s, 1H), 3.84 – 3.43 (m, 10H), 3.29 – 3.05 (m, 4H), 2.74 – 2.52 (m, 4H), 2.40 (s, 2H), 1.58 – 1.43 (m, 2H), 1.39 – 1.25 (m, 2H), 1.17 – 0.53 (m, 6H).

Example 228

1-[4-({3-[(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)methyl]azacyclobutan-1-yl}methyl)piperidin-1-yl]ethan-1-one **228**



Step 1

6-bromo-8-chloro-1-fluoro-3-methylimidazo[1,5-a]pyridine **228a**

Compound **73a** (11.63 g, 47.37 mmol) was dissolved in acetonitrile (500 mL), followed by the addition of pyridine (5.62 g, 71.06 mmol). The mixture was cooled to -10℃, a Selectfluor fluridizer (16.78 g, 47.37 mmol) was added, and the mixture was stirred at -10℃ to allow for reacting for 0.5 hours. A saturated aqueous sodium thiosulfate solution (300 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (300 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **228a** (4.8 g, 18.22 mmol, yield: 38.45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.65 (s, 1H), 2.56 (s, 3H).

Step 2

3-({8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}methylene)azacyclobutan-1-tert-butyl carboxylate **228b**

Compound **228a** (800 mg, 3.04 mmol), 3-[(tetramethyl-1,3,2-dioxaboran-2-yl)methylene]azacyclobutan-1-tert-butyl carboxylate **206c** (941.02 mg, 3.19 mmol) and sodium carbonate (965.39 mg, 9.11 mmol) were dissolved in dioxane (9 mL) and water (1.8 mL). Pd (dppf)Cl_2 (222.15 mg, 303.61 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **228b** (770 mg, 2.19 mmol, yield: 72.09%).

MS m/z (ESI): 352.1 [M+1]

Step 3

3-[(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)methylene]azacyclobutan-1-tert-butyl carboxylate **228c**

Compound **228b** (200 mg, 568.5 μmol) and Compound **197b** (216.82 mg, 596.93 μmol) were dissolved in dioxane (4 mL) and water (1.0 mL). Potassium phosphate (362.02 mg, 1.71 mmol) and Pd(dtbpf)Cl_2 (37.05 mg, 56.85 μmol) were added, and the mixture was stirred at 90 °C under a nitrogen atmosphere to allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **228c** (220 mg, 398.11 μmol, yield: 70.03%).

MS m/z (ESI): 553.2 [M+1]

Step 4

3-[(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **228d**

Compound **228c** (120 mg, 217.15 μmol) was dissolved in methanol (4.0 mL), followed by the addition of 10% Pd/C(100 mg, 939.67 μmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (15 psi), and the mixture was stirred at room temperature for 2.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **228d** (110 mg, 198.33 μmol, yield: 91.33%) as yellow solid.

MS m/z (ESI): 555.3 [M+1]

Step 5

(3*R*,5*R*)-4-(2-{6-[(azacyclobutan-3-yl)methyl]-3-methylimidazo[1,5-a]pyridin-8-yl}-5-fluorobenzoyl)-3,5-

dimethylmorpholine **228e**

Compound **228d** (110 mg, 198.33 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a saturated aqueous sodium bicarbonate solution (10.0 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **228e** (90 mg, 198.01 μmol, yield: 99.84%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 455.2 [M+1]

Step 6

1-[4-({3-[(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)methyl]azacyclobutan-1-yl}methyl)piperidin-1-yl]ethan-1-one **228**

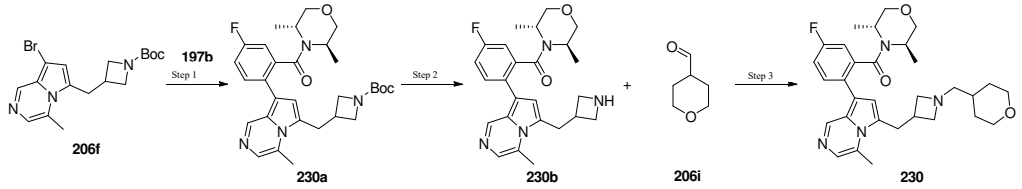
Compound **228e** (90 mg, 198.01 μmol) and Compound **189a** (46.10 mg, 297.02 μmol) were dissolved in methanol (2.0 mL). Acetic acid (11.89 mg, 198.01 μmol) was added, and the mixture was stirred for 0.5 hour. Sodium cyanoborohydride (37.33 mg, 594.04 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 8%-38%), to obtain the title Compound **228** (33.84 mg, 57.00 μmol, yield: 28.78%)

MS m/z (ESI): 594.2[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.54 – 7.33 (m, 3H), 6.42 – 6.19 (m, 1H), 4.36 – 4.27 (m, 1H), 3.80 – 3.70 (m, 2H), 3.42 – 3.16 (m, 5H), 2.98 – 2.90 (m, 3H), 2.76 – 2.67 (m, 3H), 2.59 – 2.53 (m, 3H), 2.36 – 2.30 (m, 2H), 2.09 – 2.07 (m, 2H), 1.98 – 1.94 (m, 3H), 1.69 – 1.60 (m, 2H), 1.56 – 1.45 (m, 1H), 1.19 – 0.56 (m, 9H).

Example 230

(3*R*,5*R*)-4-{5-fluoro-2-[4-methyl-6-({1-[(oxacyclobutan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]benzoyl}-3,5-dimethylmorpholine **230**



Step 1

3-[(8-{2-[(3*R*,5*R*)-3,5-dimethylmorpholin-4-carbonyl]-4-fluorophenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **230a**

Compound **206f** (170 mg, 447.04 μmol), Compound **197b**(178.62 mg, 491.74 μmol) and potassium phosphate (237.23 mg, 1.12 mmol) were dissolved in dioxane (2 mL) and water (0.3 mL). Pd(dtbpf)Cl_2 (29.14 mg, 44.70 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **230a** (220 mg, 409.96 μmol, yield: 91.71%) as yellow solid.

MS m/z (ESI): 537.3 [M+1]

Step 2

(3*R*,5*R*)-4-(2-{6-[(azacyclobutan-3-yl)methyl]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-5-fluorobenzoyl)-3,5-dimethylmorpholine **230b**

Compound **230a** (110 mg, 204.98 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **230b** (115 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 437.1 [M+1]

Step 3

(3*R*,5*R*)-4-{5-fluoro-2-[4-methyl-6-({1-[(oxacyclobutan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]benzoyl}-3,5-dimethylmorpholine **230**

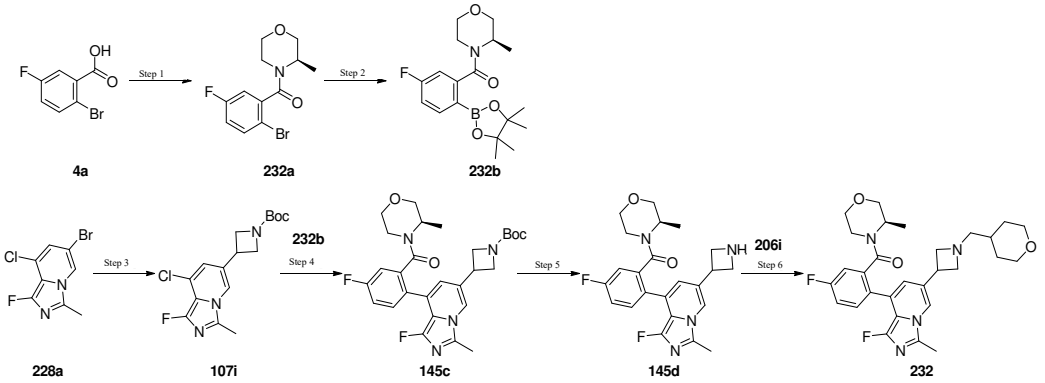
Compound **230b** (110.11 mg, 200 μmol, trifluoroacetate) and Compound **206i** (34.24 mg, 300.00 μmol) were dissolved in methanol (1.0 mL). Triethylamine (30.36 mg, 300.00 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (37.71 mg, 600.00 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 27%-57%), to obtain the title Compound **230** (27.59 mg, 51.60 μmol, yield: 25.80%)

MS m/z (ESI): 535.3[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 – 8.24 (m, 1H), 7.59 – 7.17 (m, 4H), 6.75 – 6.48 (m, 1H), 3.83 – 3.75 (m, 2H), 3.73 – 3.47 (m, 4H), 3.43 – 3.37 (m, 2H), 3.26 – 3.11 (m, 4H), 2.89 – 2.65 (m, 7H), 2.25 (d, J = 6.8 Hz, 2H), 1.62 – 0.33 (m, 12H).

Example 232

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **232**



Step 1

(3*R*)-4-(2-bromo-5-fluorobenzoyl)-3-methylmorpholine **232a**

2-Bromo-5-fluoro-benzoic acid **4a** (40 g, 182.64 mmol) was dissolved in dichloromethane (500 mL), followed by the addition of DIPEA (70.82 g, 547.93 mmol) and HATU (83.34 g, 219.17 mmol). The reaction mixture was stirred for 5 min, followed by the addition of (3*R*)-3-methylmorpholine (20.32 g, 200.91 mmol). The mixture was stirred at 50℃ for 2 hours. The reaction was quenched with a saturated aqueous sodium carbonate solution (300 mL), and the reaction mixture was extracted with dichloromethane (200 ml × 3). The organic phase was washed with 1M HCl aqueous solution (200 ml×3), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the crude product of title Compound **232a** (55 g, 182.04 mmol, yield99.67%) as yellow oil.

MS m/z (ESI): 301.9 [M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzoyl]-3-methylmorpholine **232b**

Compound **232a** (50 g, 165.49 mmol), potassium acetate (48.72 g, 496.46 mmol) and bis(pinacolato)diboron (100 g, 393.80 mmol) were dissolved in DMSO (700 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (10 g, 13.67 mmol) was added, and the mixture was stirred at 110°C to allow for reacting for 6.0 hours. After the mixture was cooled to room temperature, 500 mL of water was added, and the mixture was extracted with ethyl acetate (400 ml × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure to obtain a crude product. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **232b** (36 g, 103.09 mmol, yield: 62.3%) as colorless oil.

MS m/z (ESI): 349.9 [M+1]

Step 3

3-{8-chloro-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **107i**

Under the protection of nitrogen, 1,2-dibromoethane (2.59 g, 13.78 mmol) was dissolved in DMAc (250 mL), followed by the addition of zinc powder (8.32 g, 127.16 mmol). The mixture was stirred at 70°C for 10 min, and then cooled to room temperature, followed by the slow dropwise addition of TMSCl (1.15 g, 10.60 mmol) to the reaction mixture, and after the dropwise addition, the reaction mixture was further stirred at 25° for 20 min. Then, the solution of 3-iodoazacyclobutan-1-tert-butyl carboxylate (30 g, 105.97 mmol) in DMAc (50 mL) was dropwise added to the reaction mixture. The reaction mixture was warmed to 35°C and stirred for 12 hours, until the disappearance of noticeable solid precipitates in the mixture. The reaction mixture was cooled to 25°C, followed by the addition of

Compound **228a** (20 g, 75.90 mmol), Pd_2 (dba)$_3$ (5 g, 8.70 mmol) and tri(2-furyl)phosphine (2.46 g, 10.60 mmol) to the reaction, and the reaction mixture was then subjected to nitrogen substitution three times, warmed to 70°C and stirred to allow for reacting for 5 hours. The reaction mixture was cooled to room temperature, followed by adding water (500 mL) and extracting with ethyl acetate (500 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107i** (12.7 g, 37.38 mmol, yield: 35.27%) as yellow solid.
MS m/z (ESI): 340.1 [M+1]

Step 4

3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **145c**

Compound **107i** (12.7 g, 37.38 mmol), Compound **232b**(19.58 g, 56.06 mmol) and potassium phosphate (23.80 g, 112.13 mmol) were dissolved in dioxane (150 mL) and water (30 mL). Pd(dtbpf)Cl_2 (2.44 g, 3.74 mmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, water (200 mL) was added, and the mixture was extracted with ethyl acetate (150 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **145c** (18.87 g, 35.84 mmol, yield: 95.88%).
MS m/z (ESI): 527.3 [M+1]

Step 5

(3*R*)-4-{2-[6-(azacyclobutan-3-yl)-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **145d**

Compound **145c** (150 mg, 284.86 μmol) was dissolved in methane dioxide (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of water (5.0 mL), and the reaction mixture was then regulated to PH > 7 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **145d** (121.48 mg, 284.86 μmol, yield: 100%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 427.1 [M+1]

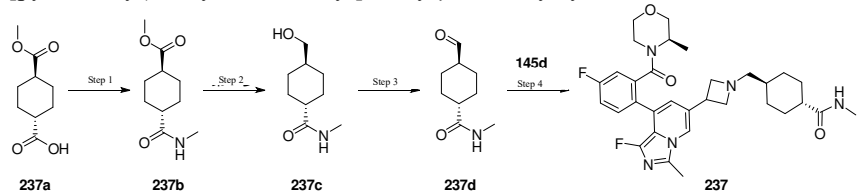
Step 6

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **232**

The crude product of Compound **145d** (121.48 mg, 284.86 μmol) and Compound **206i** (48.77 mg, 427.29 μmol) were dissolved in methanol (3.0 mL). Acetic acid (17.11 mg, 284.86 μmol) was added, and the mixture was stirred for 1.0 hour. Sodium cyanoborohydride (53.70 mg, 854.57 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **232** (17.68 mg, 33.70 μmol, yield: 11.83%) as yellow solid.
MS m/z (ESI): 525.3[M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 9.2 Hz, 1H), 7.64 – 7.52 (m, 1H), 7.39 – 7.16 (m, 2H), 6.87 – 6.57 (m, 1H), 4.09 – 3.90 (m, 4H), 3.82 – 3.67 (m, 4H), 3.62 – 3.56 (m, 1H), 3.45 – 3.36 (m, 4H), 2.60 (s, 3H), 2.50 (d, J = 6.4 Hz, 2H), 1.73 – 1.62 (m, 4H), 1.50 – 1.39 (m, 1H), 1.36 – 1.23 (m, 4H), 1.20 – 1.12 (m, 1H), 0.81 – 0.80 (m, 1H), 0.80 (d, J = 5.6 Hz, 1H).

Example 237

(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}-*N*-methylcyclohexan-1-formamide **237**



Step 1

(1*r*,4*r*)-4-(methylaminoformyl)cyclohexan-1-methyl carboxylate **237b**

(1*r*,4*r*)-4-(methoxycarbonyl)cyclohexan-1-carboxylic acid **237a** (1 g, 5.37 mmol) was dissolved in DCM (10 mL), followed by the addition of HATU(2.45 g, 6.44 mmol) and triethylamine (1.63 g, 16.11 mmol). The reaction mixture was stirred for 5 min, followed by the addition of methylamine (435.12 mg, 6.44 mmol). The reaction mixture was stirred at 25℃ for 12.0 hours. A saturated aqueous sodium carbonate solution (25 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **237b** (920 mg, 4.62 mmol, yield: 85.98%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 4.0 Hz, 1H), 3.58 (s, 3H), 2.54 (d, J = 4.4 Hz, 3H), 2.31 – 2.20 (m, 1H), 2.08 – 1.97 (m, 1H), 1.95 – 1.86 (m, 2H), 1.77 – 1.69 (m, 2H), 1.43 – 1.22 (m, 4H).

Step 2

(1*r*,4*r*)-4-(hydroxylmethyl)-*N*-methylcyclohexan-1-formamide **237c**

Compound **237b** (920 mg, 4.62 mmol) was dissolved in ethanol (19.88 mL). Under a nitrogen atmosphere, the mixture was cooled to -10°C, sodium borohydride (680 mg, 17.97 mmol) was added slowly, and the mixture was warmed to room temperature and stirred to allow for reacting for 11 hours. Calcium chloride (1.02 g, 9.23 mmol) was supplemented, and the mixture was warmed to 55°C and further stirred to allow for reacting for 2 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (20 mL) and filtered, and the filtrate was extracted with ethyl acetate (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **237c** (110 mg, 642.39 μmol, yield: 13.91%) as yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 4.0 Hz, 1H), 4.42 – 4.27 (m, 1H), 3.26 – 3.12 (m, 2H), 2.56 – 2.51 (m, 3H), 2.03 – 1.94 (m, 1H), 1.78 – 1.66 (m, 4H), 1.35 – 1.24 (m, 3H), 0.91 – 0.80 (m, 2H).

Step 3

(1*r*,4*r*)-4-formyl-*N*-methylcyclohexan-1-formamide **237d**

Compound **237c** (100.00 mg, 583.99 μmol) was dissolved in DMSO(1 mL). Under a nitrogen atmosphere, the mixture was cooled to 0°C, and a Burgess reagent (180.92 mg, 759.19 μmol) was added slowly. The reaction mixture was stirred at room temperature to allow for reacting for20 min. In an ice water bath, water (5 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **237d** (97 mg, 573.22 μmol, yield: 98.16%) as yellow oil. The crude product was directly used in the next step of reaction without purification.

Step 4

(1*r*,4*r*)-4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}-*N*-methylcyclohexan-1-formamide **237**

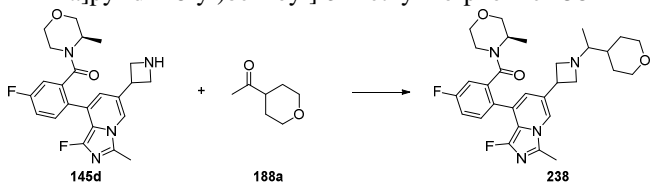
Compound **145d** (81 mg, 189.04 μmol) and Compound **237d** (38.39 mg, 226.85 μmol) were dissolved in methanol (2.0 mL). Triethylamine (57.39 mg, 567.13 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (36.00 mg, 572.80 μmol) was added, and the mixture was stirred at room temperature for 11.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 27%-57%) two times, to obtain the title Compound **237** (13 mg, 22.43 μmol, yield: 11.86%) as yellow solid.

MS m/z (ESI): 580.3[M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.68 – 8.43 (m, 1H), 7.92 (s, 1H), 7.67 – 7.50 (m, 1H), 7.44 – 7.16 (m, 2H), 6.89 – 6.53 (m, 1H), 4.66 – 4.25 (m, 3H), 4.15 – 3.86 (m, 3H), 3.84 – 3.35 (m, 3H), 3.23 – 2.83 (m, 4H), 2.70 (s, 3H), 2.62 (s, 3H), 2.31 (s, 6H), 1.70 – 1.58 (m, 1H), 1.57 – 1.40 (m, 2H), 1.38 – 0.96 (m, 4H), 0.76 (s, 1H).

Example 238

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **238**



Compound **145d** (81 mg, 189.94 μmol) and Compound **188a** (26.78 mg, 208.93 μmol) were dissolved in methanol (1.0 mL). Zinc chloride (51.78 mg, 379.87 μmol) was added, and the mixture was stirred at 55℃ for 1.0 hour. After

cooling, sodium cyanoborohydride (36.17 mg, 575.51 μmol) was added, and the mixture was further stirred at 55℃ for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 31%-61%), to obtain the title Compound **238** (50 mg, 92.83 μmol, yield: 48.87 %) as yellow solid.

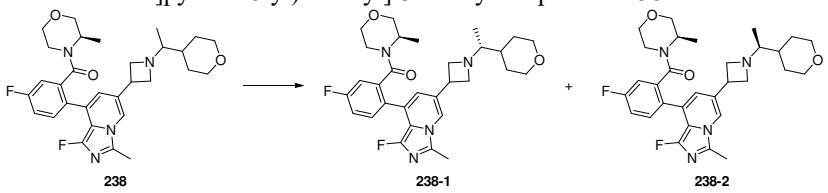
MS m/z (ESI): 539.4[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.69 (m, 1H), 7.68 – 7.16 (m, 3H), 6.93 – 6.35 (m, 1H), 4.50 – 3.37 (m, 9H), 3.28 – 2.63 (m, 7H), 2.54 (s, 3H), 2.26 – 2.06 (m, 1H), 1.68 – 1.42 (m, 2H), 1.38 – 1.00 (m, 5H), 0.91 – 0.56 (m, 4H).

Examples 238-1 and 238-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*)-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **238-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*S*)-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **238-2**



Compound **238** (221 mg, 410 μmol) was purified by the chiral preparative SFC (preparative column: Daicel ChiralPak AD (250*30mm, 10um); mobile phase: CO_2-EtOH (0.1% ammonia water); elution gradient: 15%), to obtain the title Compounds **238-1** (67.24 mg, 124.84 μmol, yield: 30.42 %) and **238-2** (61.24 mg, 113.70 μmol, yield: 27.71 %).

Compound 238-1:

MS m/z (ESI): 539.3[M+1]

chiral HPLC: retention time: 1.260 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05%DEA); elution gradient: 5%-40%;

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.73 (m, 1H), 7.68 – 7.18 (m, 3H), 6.92 – 6.46 (m, 1H), 4.41 – 3.41 (m, 9H), 3.29 – 2.84 (m, 7H), 2.55 (s, 3H), 2.26 – 2.06 (m, 1H), 1.63 – 1.42 (m, 2H), 1.35 – 1.06 (m, 5H), 0.84 – 0.68 (m, 4H).

Compound 238-2:

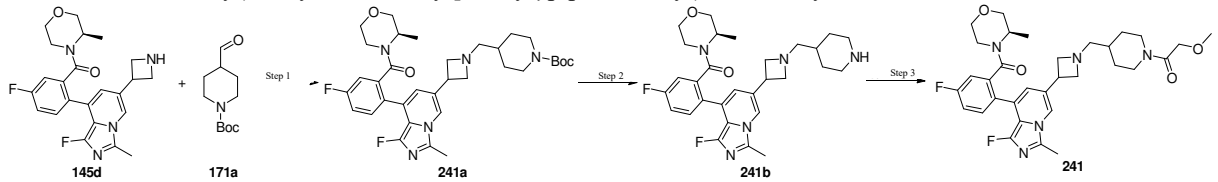
MS m/z (ESI): 539.4[M+1]

Chiral HPLC: retention time: 1.157 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO2-EtOH (0.05%DEA); elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 7.76 (m, 1H), 7.67 – 7.18 (m, 3H), 7.02 – 6.30 (m, 1H), 4.72 – 3.35 (m, 9H), 3.29 – 2.74 (m, 7H), 2.54 (s, 3H), 2.21 – 1.99 (m, 1H), 1.62 – 1.43 (m, 2H), 1.35 – 1.26 (m, 2H), 1.24 – 1.10 (m, 3H), 0.87 – 0.59 (m, 4H).

Example 241

1-(4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-yl)-2-methoxyethan-1-one **241**



Step 1

4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-tert-butyl carboxylate **241a**

Compound **145d** (140 mg, 328.29 μmol), 4-formylpiperidin-1-tert-butyl formate **171a** (105.02 mg, 492.43 μmol) and acetic acid (19.71 mg, 328.29 μmol) were dissolved in methanol (2.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (61.89 mg, 984.86 μmol) was added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative

thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **241a** (140 mg, 224.46 μmol, yield: 68.37%) as yellow solid.
MS m/z (ESI): 624.3 [M+1]
1.69 – 1.61 (m, 2H), 1.38 (s, 12H), 1.05 – 0.91 (m, 6H).

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(piperidin-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **241b**

Compound **241a** (140 mg, 224.46 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **241b** (100 mg, 190.98 μmol, yield: 85.09%) as yellow solid. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 524.2 [M+1]

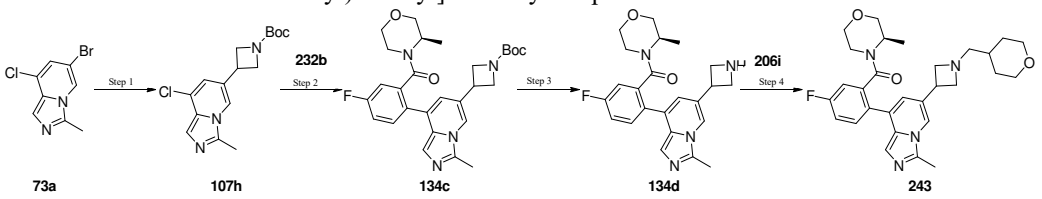
Step 3

1-(4-{[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-yl)-2-methoxyethan-1-one **241**

Triethylamine (47.61 mg, 470.49 μmol) and Compound **241b** (100 mg, 156.83 μmol, trifluoroacetate) were dissolved in dichloromethane (2.0 mL), and stirred at room temperature for 10 min, followed by the addition of 2-methoxyacetyl chloride (20.42 mg, 188.15 μmol). The reaction mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 24%-54%), to obtain the title Compound **241** (7.79 mg, 13.08 μmol, yield: 8.34 %) as yellow solid.
MS m/z (ESI): 596.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (s, 1H), 7.65 – 7.51 (m, 1H), 7.38 – 7.17 (m, 2H), 6.90 – 6.60 (m, 1H), 4.59 – 4.41 (m, 2H), 4.19 – 4.08 (m, 2H), 3.89 – 3.69 (m, 5H), 3.65 – 3.47 (m, 2H), 3.40 – 3.37 (m, 3H), 3.29 – 3.23 (m, 3H), 3.09 – 2.96 (m, 2H), 2.70 – 2.57 (m, 4H), 2.53 – 2.45 (m, 2H), 1.87 – 1.76 (m, 2H), 1.74 – 1.64 (m, 1H), 1.38 – 1.02 (m, 5H), 0.81 – 0.57 (m, 1H).

Example 243

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **243**



Step 1

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **107h**

Under the protection of nitrogen, 1,2-dibromoethane (120.77 mg, 642.87 μmol) was dissolved in DMAc (8.0 mL), followed by the addition of zinc powder (388.04 mg, 5.93 mmol). The mixture was stirred at 70°C for 10 min, and then cooled to room temperature, followed by the slow dropwise addition of TMSCl (53.72 mg, 494.51 μmol) to the reaction mixture, and after the dropwise addition, the reaction mixture was further stirred at 25° for 30 min. Then, the solution of 3-iodoazacyclobutan-1-tert-butyl carboxylate (1.4 g, 4.95 mmol) in DMAc (10 mL) was dropwise added to the reaction mixture. The reaction mixture was warmed to 40°C and stirred for 1 hours, until the disappearance of noticeable solid precipitates in the mixture. The reaction mixture was cooled to 25°C, followed by the addition of Compound **73a** (1.09 g, 4.45 mmol), $Pd_2(dba)_3$ (284.35 mg, 494.51 μmol) and tri(2-furyl)phosphine (114.81 mg, 494.51 μmol) to the reaction, and the reaction mixture was then subjected to nitrogen substitution three times, warmed to 70°C and stirred to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **107h** (560 mg, 1.74 mmol, yield: 35.19%) as brown oil.
MS m/z (ESI): 321.9 [M+1]

Step 2

3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-

yl)azacyclobutan-1-tert-butyl carboxylate **134c**

Compound **107h** (500 mg, 1.55 mmol), Compound **232b**(651.09 mg, 1.86 mmol) and potassium phosphate (824.52 mg, 3.88 mmol) were dissolved in dioxane (5.0 mL) and water (1.0 mL). Pd(dtbpf)Cl_2 (101.27 mg, 155.38 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **134c** (500 mg, 983.12 μmol, yield: 63.27%) as yellow solid.

MS m/z (ESI): 509.2 [M+1]

Step 3

(3*R*)-4-{2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **134d**

Compound **134c** (110 mg, 216.29 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure to obtain the crude product of title Compound **134d** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 408.9 [M+1]

Step 4

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(oxacyclohexan-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **243**

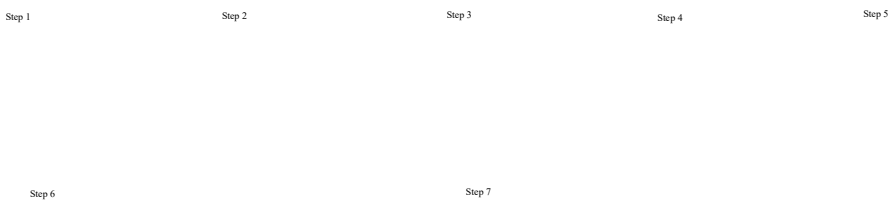
The crude product of Compound **134d** (100 mg) and Compound **206i** (36.98 mg, 324.00 μmol) were dissolved in methanol (2.0 mL). Triethylamine (32.79 mg, 324.00 μmol) was added, and the mixture was stirred at room temperature for 0.5 hour. Sodium cyanoborohydride (40.72 mg, 648.00 μmol) was added, and the mixture was stirred at room temperature for 11.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 17%-47%), to obtain the title Compound **243** (63.42 mg, 125.19 μmol, yield: 57.96 %) as yellow solid.

MS m/z (ESI): 507.4[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.88 (m, 1H), 7.81 – 7.59 (m, 1H), 7.48 – 7.25 (m, 2H), 7.13 – 6.65 (m, 2H), 4.39 – 3.76 (m, 3H), 3.72 – 3.36 (m, 5H), 3.29 – 3.07 (m, 5H), 3.02 – 2.66 (m, 2H), 2.60 (s, 3H), 2.40 – 2.23 (m, 2H), 1.94 – 0.96 (m, 8H), 0.69 – 0.37 (m, 1H).

Example 244

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **244**



Step 1

(2*S*)-2-[(1*E*)-3-ethoxy-3-oxopropyl-1-ene-1-yl]morpholin-4-tert-butyl carboxylate **244b**

(2*R*)-2-formylmorpholin-4-tert-butyl carboxylate **244a** (18 g, 83.63 mmol) were dissolved in toluene (50 mL), followed by the addition of ethyl(triphenylphosphoranylidene)acetate (29.13 g, 83.63 mmol). The reaction mixture was stirred at 90°C for 16 hours. Water (500 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (300 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **244b** (13 g, 45.56 mmol, yield: 54.48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, J = 15.8, 4.0 Hz, 1H), 6.11 (d, J = 15.6 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 4.15 – 3.75 (m, 4H), 3.57 (s, 1H), 3.02-2.60 (m, 2H), 1.47 (s, 9H), 1.29 (dd, J = 9.6, 4.6 Hz, 3H).

Step 2

(2*S*)-2-(3-ethoxy-3-oxypropyl)morpholin-4-tert-butyl carboxylate **244c**

Compound **244b** (13 g, 45.56 mmol) was dissolved in methanol (40 mL), followed by the addition of 10% Pd/C(5.53 g, 45.56 mmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (20 psi), and the mixture was stirred at 25°C for 16.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **244c** (13 g, 45.24 mmol, yield: 99.3%).

MS m/z (ESI): 310.0 [M+23]

Step 3

3-[(2*S*)-4-[(tert-butoxy)carbonyl]morpholin-2-yl]propionic acid **244d**

Under the protection of nitrogen, Compound **244c** (13 g, 45.24 mmol) was dissolved in tetrahydrofuran (120 mL) and water (30 mL), followed by the addition of lithium hydroxide (3.25 g, 135.72 mmol), and the mixture was stirred at room temperature for 4.0 hours. The reaction mixture was regulated to PH < 4 by adding a saturated aqueous citric acid solution, and extracted with ethyl acetate (300 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **244d** (11 g, 42.42 mmol, yield: 93.77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87-3.70 (m, 3H), 3.51-3.27 (m, 2H), 2.97-2.82 (m, 1H), 2.54-2.28 (m, 3H), 1.87-1.71 (m, 2H), 1.44 (s, 9H).

Step 4

(2*S*)-2-{2-[methoxy(methyl)aminoformyl]ethyl}morpholin-4-tert-butyl carboxylate **244e**

Compound **244d** (11 g, 42.42 mmol) was dissolved in DMF (130 mL), followed by the addition of HATU (24.20 g, 63.63 mmol) and *N*-methoxymethylamine (6.21 g, 63.63 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 3.0 hours. Water (1000 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (300 mL x 3). The organic phase was washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **244e** (5.0 g, 16.54 mmol, yield: 38.98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90-3.79 (m, 3H), 3.69(s, 3H), 3.52-3.45(m, 1H), 3.42-3.34(m, 1H), 3.18(s, 3H), 2.98-2.86(m, 1H), 2.65-2.51(m, 3H), 1.84-1.76(m, 2H), 1.46(s, 9H).

Step 5

(2*S*)-2-(4-methyl-3-oxopentyl)morpholin-4-tert-butyl carboxylate **244f**

Under the protection of nitrogen, Compound **244e** (550 mg, 1.82 mmol) was dissolved in tetrahydrofuran (10 mL), and cooled to -78°C. An isopropyllithium solution (1.6 M, 3.41mL) was added dropwise to the reaction mixture, after which the reaction mixture was stirred at -78°C for 4.0 hours. Water (1.0 mL) and a saturated aqueous ammonium chloride solution (1.0 mL) were added to the reaction mixture, followed by stirring for 0.5 hours and adding water (50 mL), and the reaction mixture was then extracted with ethyl acetate (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **244f** (165 mg, 578.18 μmol, yield: 31.79%) as colorless oil.

MS m/z (ESI):186.2 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (br dd, J = 2.8, 11.1 Hz, 4H), 3.44 – 3.34 (m, 1H), 3.28 – 3.18 (m, 1H), 2.93 – 2.81 (m, 1H), 2.56 – 2.51 (m, 2H), 2.51 – 2.48 (m, 1H), 1.76 – 1.68 (m, 2H), 1.39 (s, 9H), 1.03 (d, J = 7.0 Hz, 6H).

Step 6

(2S)-2-{3-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl}morpholin-4-tert-butyl carboxylate **244g**

Compound **145d** (121.48 mg, 284.86 μmol) and Compound **244f** (89.42 mg, 313.34 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (77.65 mg, 569.72 μmol), and the mixture was stirred at 25°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (53.70 mg, 854.57 μmol), allowing for reacting at 25°C for 1.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **244g** (198 mg, 284.55 μmol, yield: 99.89%).

MS m/z (ESI):696.2 [M+1]

Step 7

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **244**

Compound **244g** (198.00 mg, 284.55 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (5.0 mL) and water (5.0 mL), and the reaction mixture was then regulated to PH >7 with a 10% aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **244** (57.3 mg, 96.19 μmol, yield: 33.8%).

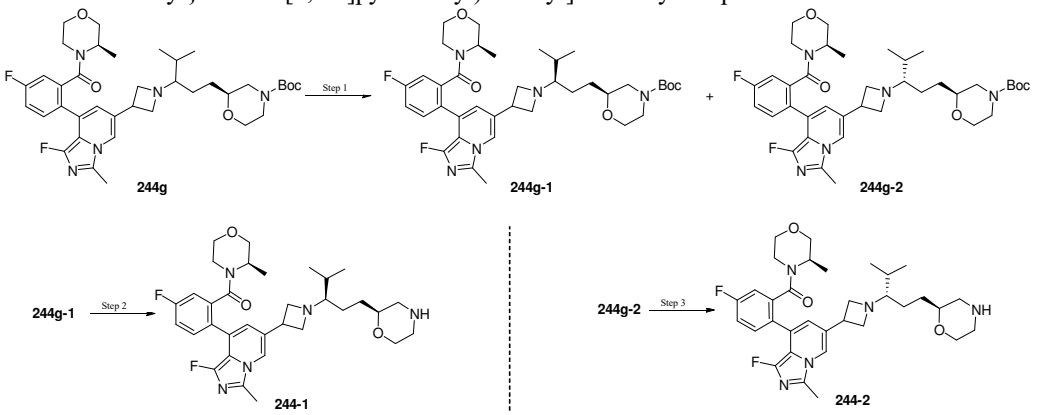
MS m/z (ESI):596.1 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, J = 10.0 Hz, 1H), 7.54 – 7.41 (m, 1H), 7.27 – 7.06 (m, 2H), 6.75 – 6.49 (m, 1H), 3.85 – 3.63 (m, 4H), 3.61 – 3.40 (m, 4H), 3.29 – 3.23 (m, 2H), 2.98 – 2.75 (m, 4H), 2.58 – 2.51 (m, 1H), 2.50 (s, 3H), 2.25 (s, 1H), 2.08 – 1.92 (m, 1H), 1.82 – 1.71 (m, 1H), 1.60 – 1.34 (m, 4H), 1.30 – 1.14 (m, 3H), 1.06 (d, J = 5.6 Hz, 1H), 0.87 – 0.78 (m, 6H), 0.74 – 0.64 (m, 1H).

Examples 244-1 and 244-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **244-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **244-2**



Step 1

(2*S*)-2-[(3*R*)-3-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **244g-1**

(2*S*)-2-[(3*S*)-3-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **244g-2**

Compound **244g** (100 mg, 143.71 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALPAK IG (250 mm * 30 mm,10 um), mobile phase: n-hexane-isopropanol/acetonitrile (0.1%isopropylamine); elution gradient: 15%), to obtain the title Compounds **244g-1** (25 mg, 35.93 μmol, yield: 25.0%) and **244g-2** (43 mg, 61.80 μmol, yield: 43%).

Single-configuration Compound 244g-1:

MS m/z (ESI):696.2 [M+1]

Chiral HPLC analysis: retention time: 3.365 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-ethanol/acetonitrile (0.05% isopropylamine): elution gradient: 10%.

Single-configuration Compound 244g-2:

MS m/z (ESI):696.5 [M+1]

Chiral HPLC analysis: retention time: 4.023 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-ethanol/acetonitrile (0.05% isopropylamine): elution gradient: 10%.

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **244-1**

Compound **244g-1** (25.00 mg, 35.93 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for

reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (5.0 mL) and water (5.0 mL), and the reaction mixture was then regulated to PH >7 with a 10% aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%). The title Compound **244-1** (5.45 mg, 9.15 μmol, yield: 25.46%) was obtained as yellow solid.

Single-configuration Compound 244-1:

MS m/z (ESI):596.4 [M+1]

Chiral SFC: retention time: 1.144 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, J = 13.0 Hz, 1H), 7.67 – 7.53 (m, 1H), 7.41 – 7.18 (m, 2H), 6.87 – 6.54 (m, 1H), 4.58 – 4.05 (m, 1H), 3.87 – 3.54 (m, 7H), 3.37 (s, 2H), 3.28 – 3.20 (m, 2H), 3.19 – 3.11 (m, 1H), 3.07 – 2.91 (m, 1H), 2.83 (d, J = 12.4 Hz, 1H), 2.76 (d, J = 3.6 Hz, 2H), 2.62 (s, 3H), 2.53 – 2.39 (m, 1H), 2.23 (s, 1H), 1.93 – 1.79 (m, 1H), 1.67 – 1.55 (m, 1H), 1.53 – 1.41 (m, 2H), 1.37 – 1.25 (m, 2H), 1.19 (d, J = 4.2 Hz, 1H), 1.06 – 0.31 (m, 8H).

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-4-methyl-1-[(2*S*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **244-2**

Compound **244g-2** (30.00 mg, 43.11 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (5.0 mL) and water (5.0 mL), and the reaction mixture was then regulated to PH >7 with a 10% aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 27%-57%). The title Compound **244-2** (8.54 mg, 14.34 μmol, yield: 33.25%) was obtained as yellow solid.

Single-configuration Compound 244-2:

MS m/z (ESI):596.4 [M+1]

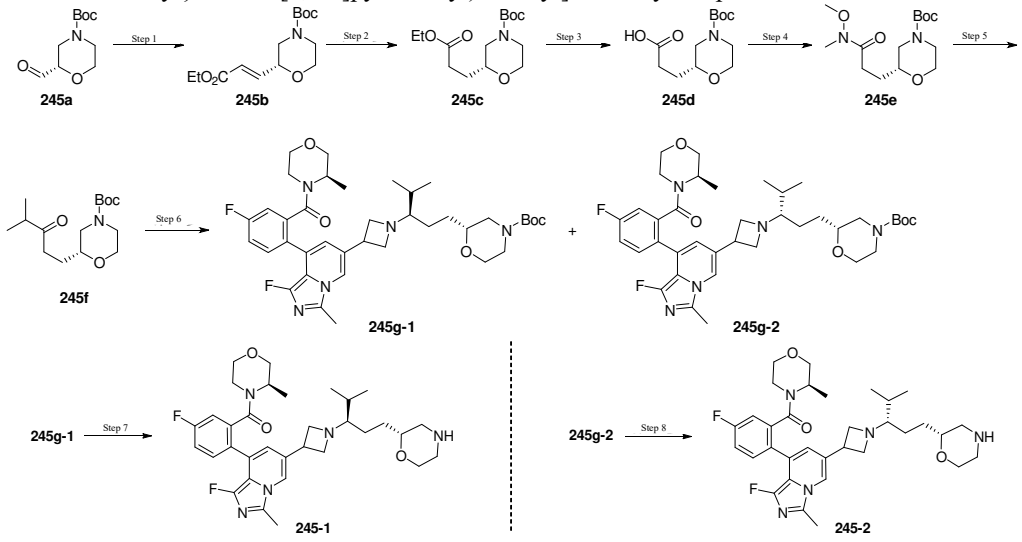
Chiral SFC: retention time: 1.224min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.89 – 7.77 (m, 1H), 7.70 – 7.52 (m, 1H), 7.44 – 7.18 (m, 2H), 6.89 – 6.61 (m, 1H), 4.64 – 4.08 (m, 2H), 3.87 – 3.56 (m, 7H), 3.50 – 3.37 (m, 2H), 3.25 (d, J = 6.4 Hz, 2H), 3.20 – 3.09 (m, 1H), 3.07 – 2.93 (m, 1H), 2.92 – 2.83 (m, 1H), 2.79 (d, J = 5.6 Hz, 2H), 2.62 (s, 3H), 2.48 (t, J = 11.4 Hz, 1H), 2.24 (s, 1H), 1.93 – 1.81 (m, 1H), 1.52 – 1.41 (m, 3H), 1.36 – 1.26 (m, 1H), 1.24 – 1.13 (m, 1H), 1.00 – 0.50 (m, 8H).

Examples 245-1 and 245-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-4-methyl-1-[(2*R*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **245-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-4-methyl-1-[(2*R*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **245-2**



Step 1

(2*R*)-2-[(1*E*)-3-ethoxy-3-oxopropyl-1-ene-1-yl]morpholin-4-tert-butyl carboxylate **245b**

(2*S*)-2-formylmorpholin-4-tert-butyl carboxylate **245a** (20 g, 92.92 mmol) was dissolved in toluene (20 mL), followed by the addition of ethyl(triphenylphosphoranylidene)acetate (32.37 g, 92.92 mmol). The reaction mixture was stirred at 90°C for 16 hours. Water (1000 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (500 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **245b** (15 g, 52.57 mmol, yield: 56.58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, J = 15.8, 4.0 Hz, 1H), 6.11 (d, J = 15.6 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 4.15 – 3.75 (m, 4H), 3.57 (s, 1H), 3.02-2.60 (m, 2H), 1.47 (s, 9H), 1.29 (dd, J = 9.6, 4.6 Hz, 3H).

Step 2

(2*R*)-2-(3-ethoxy-3-oxypropyl)morpholin-4-tert-butyl carboxylate **245c**

Compound **245b** (15.7 g, 55.02 mmol) was dissolved in methanol (160 mL), followed by the addition of 10% Pd/C(6.68 g, 55.02 mmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (20 psi), and the mixture was stirred at 25°C for 16.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **245c** (13 g, 45.24 mmol, yield: 82.22%).

MS m/z (ESI): 310.1 [M+23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, J = 7.2 Hz, 2H), 3.98-3.72 (m, 3H), 3.50-3.43 (m, 1H), 3.39-3.31 (m, 1H), 2.97-2.84 (m, 1H), 2.69-2.54 (m, 1H), 2.52 – 2.32 (m, 2H), 1.77 (dt, J = 15.2, 7.8 Hz, 2H), 1.46 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H).

Step 3

3-[(2*R*)-4-[(tert-butoxy)carbonyl]morpholin-2-yl]propionic acid **245d**

Under the protection of nitrogen, Compound **245c** (15.7 g, 54.64 mmol) was dissolved in tetrahydrofuran (160 mL) and water (40 mL), followed by the addition of lithium hydroxide (3.93 g, 163.91 mmol), and the mixture was stirred at room temperature for 3.0 hours. The reaction mixture was regulated to PH < 4 by adding a saturated aqueous citric acid solution, and extracted with ethyl acetate (300 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **245d** (13 g, 50.14 mmol, yield: 91.76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.70 (m, 3H), 3.51 – 3.27 (m, 2H), 2.97-2.82 (m, 1H), 2.54 – 2.28 (m, 3H), 1.87-1.71 (m, 2H), 1.44 (s, 9H).

Step 4

(2*R*)-2-{2-[methoxy(methyl)aminoformyl]ethyl}morpholin-4-tert-butyl carboxylate **245e**

Compound **245d** (2 g, 7.71 mmol) was dissolved in DCM (20 mL), followed by the addition of HATU (4.40 g, 11.57 mmol), DIPEA(2.99 g, 23.14 mmol) and *N*-methoxymethylamine (1.13 g, 11.57 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 3.0 hours. Water (100 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL x 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **245e** (1.0 g, 3.31 mmol, yield: 42.88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90-3.79 (m, 3H), 3.69(s, 3H), 3.52-3.45(m, 1H), 3.42-3.34(m, 1H), 3.18(s, 3H), 2.98-2.86(m, 1H), 2.65-2.51(m, 3H), 1.84-1.76(m, 2H), 1.46(s, 9H).

Step 5

(2*R*)-2-(4-methyl-3-oxopentyl)morpholin-4-tert-butyl carboxylate **245f**

Under the protection of nitrogen, Compound **245e** (200.00 mg, 661.45 μmol) was dissolved in tetrahydrofuran (10 mL), and cooled to -65°C. An isopropyllithium solution (1.6 M, 1.24 mL) was added dropwise to the reaction mixture, after which the reaction mixture was stirred at -65°C for 4.0 hours. Water (1.0 mL) and a saturated aqueous ammonium chloride solution (1.0 mL) were added to the reaction mixture, followed by stirring for 0.5 hours and adding water (50 mL), and the reaction mixture was then extracted with ethyl acetate (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **245f** (130 mg, 455.54 μmol, yield: 68.87%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 – 3.74 (m, 3H), 3.47 – 3.37 (m, 1H), 3.27 (t, J = 9.6 Hz, 1H), 2.96 – 2.78 (m, 1H), 2.63 – 2.45 (m, 4H), 1.81 – 1.69 (m, 1H), 1.67 – 1.54 (m, 1H), 1.43 (s, 9H), 1.06 (d, J = 7.2 Hz, 6H).

Step 6

(2*R*)-2-[(3*R*)-3-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-

a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **245g-1**
(2*R*)-2-[(3*S*)-3-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **245g-2**

Compound **145d** (178 mg, 417.39 μmol) and Compound **245f**(131.03 mg, 459.13 μmol) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$ (170.67 mg, 1.25 mmol), and the mixture was stirred at 25°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (78.69 mg, 1.25 mmol), allowing for reacting at 25°C for 12 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, followed by stirring for 0.5 hours and adding water (50 mL), and the reaction mixture was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the resulting solid was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: CO_2-EtOH (0.1% diethylamide); elution gradient: 25%), to obtain the title Compounds **245g-1** (55 mg, 79.04 μmol, yield: 18.94%) and **245g-2** (52 mg, 74.73 μmol, yield: 17.90%).

Single-configuration Compound 245g-1:

MS m/z (ESI):696.3 [M+1]

Chiral HPLC analysis: retention time: 1.364 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 245g-2:

MS m/z (ESI):696.4 [M+1]

Chiral HPLC analysis: retention time: 1.210 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Step 7

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-4-methyl-1-[(2*R*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **245-1**

Compound **245g-1** (52.00 mg, 74.73 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. Dichloromethane (10 mL) and a 10% aqueous NaOH solution (20 mL) were added, and the mixture was then extracted with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-53%). The title Compound **245-1** (25.87 mg, 43.43 μmol, yield: 58.11%) was obtained as yellow oil.

Single-configuration Compound 245-1:

MS m/z (ESI):596.4 [M+1]

Chiral SFC: retention time: 1.283 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.55 – 7.35 (m, 2H), 7.25 – 6.99 (m, 2H), 6.79 – 6.54 (m, 1H), 4.66 – 4.11 (m,1H), 3.90 – 2.72 (m, 18H), 2.61 (s, 3H), 2.57 – 2.43 (m, 1H), 2.09 – 2.03 (m, 1H), 1.79 – 1.75 (m, 1H), 1.51 – 1.40 (m, 3H),1.34 – 1.14 (m, 3H), 0.94 – 0.86 (m, 6H), 0.84 – 0.60 (m, 1H).

Step 8

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-4-methyl-1-[(2*R*)-morpholin-2-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **245-2**

Compound **245g-2** (52 mg, 74.73 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (10 mL) and a 10% aqueous NaOH solution (20 mL), and the mixture was then extracted with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-53%). The title Compound **245-2** (24.67 mg, 41.41 μmol, yield: 55.42%) was obtained as yellow oil.

Single-configuration Compound 245-2:

MS m/z (ESI):596.4 [M+1]

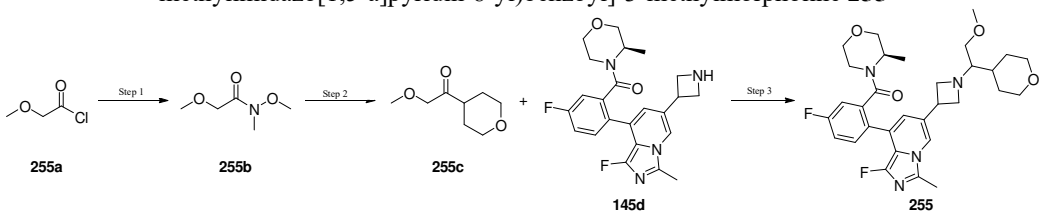
Chiral SFC: retention time: 1.138 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.31 (m, 2H), 7.24 – 7.05 (m, 2H), 6.82 – 6.50 (m, 1H), 4.92 – 4.63 (m, 1H),4.59 – 4.11 (m, 1H), 3.91 – 3.18 (m, 10H), 3.16 – 3.08 (m, 2H), 3.04 – 2.93 (m, 1H), 2.91 – 2.70 (m, 4H), 2.61 (s, 3H), 2.56 -2.42 (m, 1H), 2.10 – 2.03 (m, 1H), 1.82 – 1.77 (m, 1H), 1.52 – 1.26 (m, 5H), 1.20 – 1.04 (m, 1H), 0.90 (t, J =

6.0 Hz, 6H), 0.83- 0.58 (m, 1H).

Example 255

(3*R*)-4-[5-fluoro-2-(1-fluoro-6-{1-[2-methoxy-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **255**



Step 1

N,2-dimethoxy-*N*-methylacetamide **255b**

N-methoxymethylamine (4.49 g, 46.07 mmol, hydrochloride) and triethylamine (13.99 g, 138.22 mmol) were dissolved in dichloromethane (20 mL), and cooled to 5°C, followed by the slow dropwise addition of the solution of 2-methoxyacetyl chloride **255a** (5 g, 46.07 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3.0 hours. Water (200 mL) was added to the reaction mixture, which was then extracted with dichloromethane (100 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **255b** (2.0 g, 15.02 mmol, yield: 32.60%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 2H), 3.68 (s, 3H), 3.45 (s, 3H), 3.18 (s, 3H).

Step 2

2-methoxy-1-(oxacyclohexan-4-yl)ethan-1-one **255c**

Under the protection of nitrogen, Mg (1.24 g, 51.02 mmol) was suspended in THF (20 mL), followed by the addition of I_2 (100 mg, 394.00 μmol) and then the slow dropwise addition of the solution of 4-bromotetrahydropyran (3.5 g, 21.21 mmol) in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature for 1.0 hour. At 0°C, the prepared alkyl magnesium bromide tetrahydrofuran solution was slowly dropwise added to the solution of Compound **255b** (1.98 g, 14.85 mmol) in THF(30 mL). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with methyltert-butyl ether (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **255c** (150 mg, 948.20 μmol, yield: 4.47%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 2H), 4.04 – 3.96 (m, 2H), 3.49 – 3.40 (m, 5H), 2.84 – 2.72 (m, 1H), 1.77 – 1.70 (m, 4H).

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-6-{1-[2-methoxy-1-(oxacyclohexan-4-yl)ethyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **255**

Compound **145d** (66.82 mg, 156.68 μmol) and Compound **255c**(24.79 mg, 156.68 μmol) were dissolved in methanol (5.0 mL). Zinc chloride (64.07 mg, 470.05 μmol) was added, and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (29.54 mg, 470.05 μmol) and stirring at 50°C for 12.0 hours. A saturated aqueous ammonium chloride solution (20 mL) was added, and the reaction mixture was stirred for 0.5 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 24%-54%), to obtain the title Compound **255** (29.54 mg, 51.95 μmol, yield: 33.15%) as yellow solid.

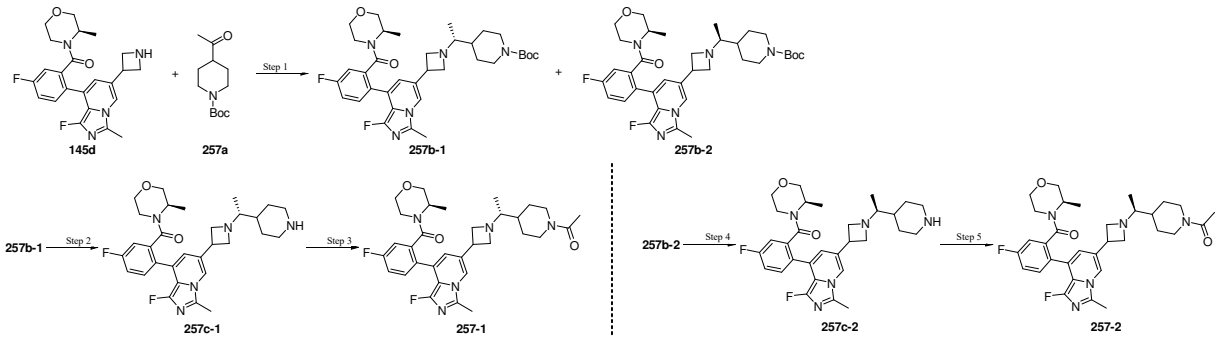
MS m/z (ESI): 569.4[M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.32 (m, 2H), 7.25 – 7.04 (m, 2H), 6.82 – 6.54 (m, 1H), 4.64 – 4.11 (m, 1H),4.05 – 3.92 (m, 2H), 3.84 – 3.49 (m, 5H), 3.48 – 2.73 (m, 13H), 2.61 (s, 3H), 2.47 – 1.98 (m, 2H), 1.80 – 1.68 (m, 1H), 1.58 -1.40 (m, 3H), 1.35 – 1.09 (m, 2H), 0.85 – 0.56 (m, 1H).

Examples 257-1 and 257-2

1-{4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}ethan-1-one **257-1**

1-{4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}ethan-1-one **257-2**



Step 1

4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-tert-butyl carboxylate **257b-1**

4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-tert-butyl carboxylate **257b-2**

Compound **145d** (137 mg, 321.25 μmol) and 4-acetylpiperidin-1-tert-butyl formate **257a** (80.32 mg, 353.38 μmol) were dissolved in methanol (10 mL), followed by the addition of zinc chloride (131.36 mg, 963.75 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (60.56 mg, 963.75 μmol) was added, and the mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, followed by stirring for 0.5 hours and dilution with water (50 mL), and the reaction mixture was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude compound was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), mobile phase: CO_2-ethanol (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **257b-1** (95 mg, 148.96 μmol, yield: 46.37%) and **257b-2** (88 mg, 137.98 μmol, yield: 42.95%).

Single-configuration Compound 257b-1:

MS m/z (ESI):638.2[M+1]

Chiral SFC analysis: retention time: 1.544 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 257b-2:

MS m/z (ESI):638.2 [M+1]

Chiral SFC analysis: retention time: 1.168 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*)-1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **257c-1**

Compound **257b-1** (95 mg, 148.96 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed once with saturated brine (50 mL), then dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **257c-1** (80 mg, 148.80 μmol, yield: 99.89%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 538.2 [M+1]

Step 3

1-{4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}ethan-1-one **257-1**

Triethylamine (45.17 mg, 446.39 μmol) and Compound **257c-1** (80 mg, 148.80 μmol) were dissolved in dichloromethane (5.0 mL), and cooled to 5°C, followed by the addition of acetyl chloride (12.85 mg, 163.68 μmol). The reaction mixture was stirred at room temperature for 2 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 22%-52%), to obtain the title Compound **257-1** (56.37 mg, 97.24 μmol, yield: 65.35%) as yellow solid.

MS m/z (ESI): 580.2 [M+1]
Chiral SFC analysis: retention time: 1.316 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.33 (m, 2H), 7.25 – 7.04 (m, 2H), 6.88 – 6.61 (m, 1H), 4.76 – 4.08 (m,2H), 3.91 – 3.51 (m, 6H), 3.42 – 2.73 (m, 7H), 2.61 (s, 3H), 2.52 – 2.38 (m, 1H), 2.35 – 2.16 (m, 1H), 2.09 (s, 3H), 1.68 – 1.50 (m, 3H), 1.34 – 1.10 (m, 4H), 0.87 – 0.56 (m, 4H).

Step 4

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*S*)-1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **257c-2**

Compound **257b-2** (88 mg, 137.98 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed once with saturated brine (50 mL), then dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **257c-2** (74 mg, 137.64 μmol, yield: 99.75%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 538.2 [M+1]

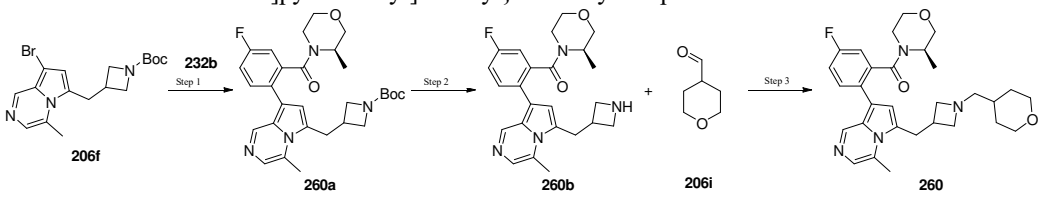
Step 5

1-{4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}ethan-1-one **257-2**

Triethylamine (41.78 mg, 412.91 μmol) and Compound **257c-2** (74 mg, 137.64 μmol) were dissolved in dichloromethane (5.0 mL), and cooled to 5°C, followed by the addition of acetyl chloride (11.88 mg, 151.40 μmol). The reaction mixture was stirred at room temperature for 2 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 22%-52%), to obtain the title Compound **257-2** (55.19 mg, 95.21 μmol, yield: 69.17 %) as yellow solid.
MS m/z (ESI): 580.3 [M+1]
Chiral SFC analysis: retention time: 1.304 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.35 (m, 2H), 7.26 – 7.07 (m, 2H), 6.88 – 6.59 (m, 1H), 4.78 – 4.10 (m,2H), 3.95 – 3.50 (m, 6H), 3.47 – 2.71 (m, 7H), 2.62 (s, 3H), 2.56 – 2.37 (m, 1H), 2.36 – 2.23 (m, 1H), 2.16 – 1.67 (m, 5H), 1.58- 1.46 (m, 1H), 1.39 – 1.11 (m, 4H), 0.89 – 0.59 (m, 4H).

Example 260

(3*R*)-4-{5-fluoro-2-[4-methyl-6-({1-[(oxacyclobutan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]benzoyl}-3-methylmorpholine **260**



Step 1

3-[(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **260a**

Compound **206f** (200 mg, 525.93 μmol), Compound **232b**(275.49 mg, 788.9 μmol) and potassium phosphate (334.91 mg, 1.58 mmol) were dissolved in dioxane (2 mL) and water (0.5 mL). Pd(dtbpf)Cl_2 (34.28 mg, 52.59 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **260a** (200 mg, 382.69 μmol, yield: 72.77%) as yellow solid.
MS m/z (ESI): 523.2 [M+1]

Step 2

(3*R*)-4-(2-{6-[(azacyclobutan-3-yl)methyl]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-5-fluorobenzoyl)-3-

methylmorpholine **260b**

Compound **260a** (92 mg, 176.04 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **260b** (70 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 423.0 [M+1]

Step 3

(3*R*)-4-{5-fluoro-2-[4-methyl-6-({1-[(oxacyclobutan-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]benzoyl}-3-methylmorpholine **260**

The crude product of Compound **260b** (70 mg) and Compound **206i** (17.87 mg, 156.57 μmol) were dissolved in methanol (2.0 mL). Triethylamine (56.17 mg, 555.06 μmol) was added, and the mixture was stirred at room temperature for 0.5 hour. Sodium cyanoborohydride (24.60 mg, 391.41 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 21%-51%), to obtain the title Compound **260** (30.27 mg, 58.14 μmol, yield: 44.56%) as yellow solid.
MS m/z (ESI): 521.3[M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 – 8.43 (m, 1H), 7.62 – 7.45 (m, 1H), 7.39 – 7.19 (m, 3H), 6.62 – 6.51 (m, 1H), 4.38 – 3.90 (m, 1H), 3.84 – 3.75 (m, 2H), 3.70 – 3.36 (m, 6H), 3.27 – 3.19 (m, 3H), 3.13 – 3.02 (m, 1H), 2.85 – 2.71 (m, 7H), 2.29 – 2.21 (m, 2H), 1.77 – 1.41 (m, 4H), 1.25 – 0.99 (m, 4H), 0.64 – 0.28 (m, 1H).

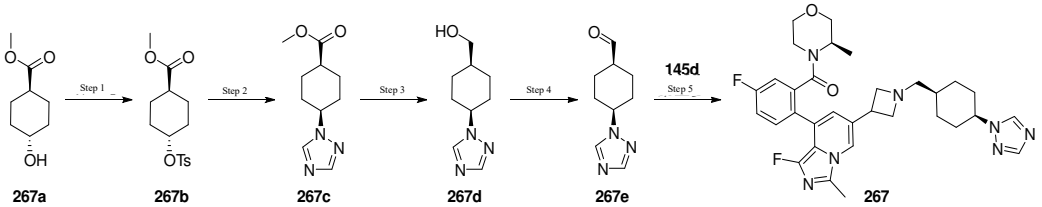
Example 266

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[1-(pyrimidin-5-yl)piperidin-4-yl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **266**

Compound **241b** (83 mg, 158.51 μmol), 5-bromopyrimidine (25.20 mg, 158.51 μmol) and sodium tert-butoxide (45.70 mg, 475.54 μmol) were dissolved in THF (2.0 mL), followed by the addition of Pd-PEPPSI-IpentCl (15.44 mg, 15.85 μmol) under the protection of nitrogen. The reaction mixture was stirred at 60°C under a nitrogen atmosphere for 12 hours. Water (15 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 22%-52%), to obtain the title Compound **266** (33 mg, 54.85 μmol, yield: 34.60 %) as yellow solid.
MS m/z (ESI): 602.3[M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 – 8.36 (m, 3H), 7.86 (s, 1H), 7.62 – 7.47 (m, 1H), 7.45 – 7.24 (m, 2H), 6.88 – 6.48 (m, 1H), 4.47 – 3.66 (m, 4H), 3.56 (s, 5H), 2.82 (s, 7H), 2.55 (s, 3H), 2.34 (d, J = 6.8 Hz, 2H), 1.90 – 1.69 (m, 2H), 1.57 – 1.39 (m, 1H), 1.31 – 1.00 (m, 4H), 0.88 – 0.48 (m, 1H).

Example 267

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **267**



Step 1

(1*r*,4*r*)-4-[(4-methylphenylsulfonyl)oxy]cyclohexan-1-methyl carboxylate **267b**

(1*r*,4*r*)-4-hydroxylcyclohexan-1-methyl carboxylate **267a** (5 g, 31.61 mmol) was dissolved in DCM (70 mL),

followed by the addition of DMAP (386.14 mg, 3.16 mmol) and triethylamine (9.59 g, 94.82 mmol). The reaction mixture was cooled to 0°C, followed by adding 4-toluensulfonyl chloride (7.23 g, 37.93 mmol). The reaction mixture was stirred at 25°C for 12.0 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **267b** (8.67 g, 27.75 mmol, yield: 87.81%) as yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 – 7.77 (m, 2H), 7.48 – 7.43 (m, 2H), 4.52 – 4.37 (m, 1H), 3.58 – 3.54 (m, 3H), 2.43 – 2.38 (m, 3H), 2.35 – 2.26 (m, 1H), 1.88 – 1.75 (m, 4H), 1.51 – 1.38 (m, 4H).

Step 2

(1*s*,4*s*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexan-1-methyl carboxylate **267c**

1*H*-1,2,4-triazole (1 g, 14.48 mmol) was dissolved in acetonitrile (40 mL), followed by the addition of Compound **267b** (3.62 g, 11.58 mmol), cesium carbonate (9.44 g, 28.96 mmol) and TBAI(534.81 mg, 1.45 mmol). The reaction mixture was heated to 85°C and stirred for 6.0 hours. The reaction mixture was filtered under a reduced pressure, and washed with ethyl acetate (100 mL), and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **267c** (1.08 g, 5.16 mmol, yield35.65%) as yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.03 – 7.77 (m, 1H), 4.43 – 4.24 (m, 1H), 3.73 – 3.50 (m, 3H), 2.73 – 2.63 (m, 1H), 2.03 – 1.86 (m, 6H), 1.75 – 1.62 (m, 2H).

Step 3

[(1*s*,4*s*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methanol **267d**

Compound **267c** (500 mg, 2.39 mmol) was dissolved in DCM(5 mL). Under a nitrogen atmosphere, the mixture was cooled to 0°C, followed by the slow dropwise addition of DIBAL-H (1 M, 4.78 mL), and the mixture was warmed to room temperature and stirred to allow for reacting for 5.0 hours. DIBAL-H (1 M, 2.0 mL) was supplemented, and the mixture was stirred at room temperature to allow for reacting for 12 hours . The reaction mixture was quenched by adding sodium sulfate decahydrate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **267d** (400 mg, 2.21 mmol, yield: 92.36%) as white solid. The crude product was directly used in the next step of reaction without purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.94 (s, 1H), 7.33 – 6.72 (m, 1H), 4.49 – 4.29 (m, 2H), 2.11 – 1.96 (m, 2H), 1.85 – 1.75 (m, 2H), 1.67 – 1.36 (m, 6H).

Step 4

(1*s*,4*s*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexan-1-formaldehyde **267e**

Compound **267d** (200 mg, 1.10 mmol) was dissolved in DMSO (4 mL). Under a nitrogen atmosphere, the mixture was cooled to 0°C, and a Burgess reagent (341.87 mg, 1.43 mmol) was added slowly. The reaction mixture was stirred at room temperature to allow for reacting for 2 hour. In an ice water bath, water (15 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **267e** (100 mg, 557.98 μmol, yield: 50.56%) as white solid. The crude product was directly used in the next step of reaction without purification.

Step 5

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **267**

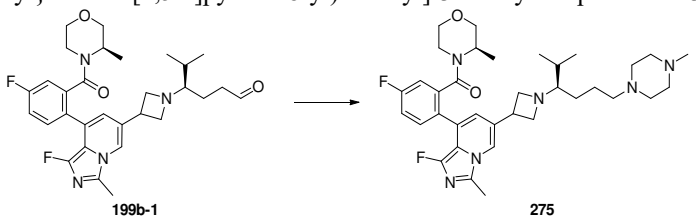
Compound **145d** (80 mg, 148.02 μmol, trifluoroacetate) and Compound **267e** (100 mg, 557.98 μmol) were dissolved in methanol (2.0 mL). Triethylamine (56.17 mg, 555.06 μmol) was added, and the mixture was stirred at room temperature for 0.5 hour. Sodium cyanoborohydride (27.90 mg, 444.05 μmol) was added, and the mixture was stirred at room temperature for 12.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 23%-53%), to obtain the title Compound **267** (10.72 mg, 18.18 μmol, yield: 12.28%) as yellow solid.

MS m/z (ESI): 590.3[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 – 8.51 (m, 1H), 8.01 – 7.78 (m, 2H), 7.63 – 7.50 (m, 1H), 7.45 – 7.25 (m, 2H), 6.78 – 6.51 (m, 1H), 4.41 – 4.11 (m, 2H), 4.00 – 3.44 (m, 6H), 3.19 – 2.89 (m, 4H), 2.56 – 2.53 (m, 3H), 2.46 – 2.28 (m, 3H), 2.07 – 1.95 (m, 2H), 1.86 – 1.76 (m, 2H), 1.65 – 1.42 (m, 5H), 1.26 – 1.03 (m, 2H), 0.83 – 0.59 (m, 1H).

Example 275

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3R)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **275**



Compound **199b-1** (230 mg, 427.01 μmol) and 1-methylpiperazine (85.54 mg, 854.02 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (25.64 mg, 427.01 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (80.50 mg, 1.28 mmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title product **275** (95 mg, 152.54 μmol, yield: 35.72%) as yellow solid.

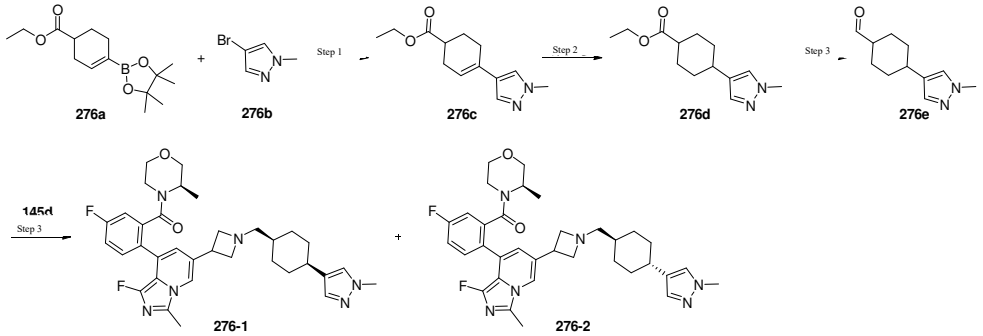
MS m/z (ESI):623.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.73 (m, 1H), 7.63 – 7.18 (m, 3H), 6.87 – 6.39 (m, 1H), 4.41 – 3.42 (m, 6H), 3.28 – 2.67 (m, 5H), 2.54 (s, 3H), 2.44 – 1.94 (m, 14H), 1.85 – 0.38 (m, 15H).

Examples 276-1 and 276-2

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **276-1**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **276-2**



Step 1

4-(1-methyl-1*H*-pyrazol-4-yl)cyclohex-3-ene-1-ethyl carboxylate **276c**

4-(Tetramethyl-1,3,2-dioxaboran-2-yl)cyclohex-3-ene-1-ethyl carboxylate **276a** (2 g, 7.14 mmol) and 4-bromo-1-methyl-1*H*-pyrazole (1.15 g, 7.14 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). Sodium carbonate (2.27 g, 21.42 mmol) and Pd(dppf)Cl_2 (522.34 mg, 713.86 μmol) were added, and the mixture was stirred at 95°C under a nitrogen atmosphere to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **176c** (750 mg, 3.20 mmol, yield: 44.84%) as yellow oil.

MS m/z (ESI): 235.2 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.29 (s, 1H), 5.98 – 5.90 (m, 1H), 4.20 – 4.10 (m, 2H), 3.86 (s, 3H), 2.63 – 2.50 (m, 1H), 2.43 – 2.33 (m, 4H), 2.15 – 2.07 (m, 1H), 1.86 – 1.74 (m, 1H), 1.29 – 1.24 (m, 3H).

Step 2

4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexan-1-ethyl carboxylate **276d**

Compound **276c** (500 mg, 2.13 mmol) was dissolved in methanol (10 mL), followed by the addition of Pd/C (51.84 mg, 213.41 μmol). Under a hydrogen atmosphere (15 Psi), the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **276d** (500 mg, 2.12 mmol, yield: 99.15%).

MS m/z (ESI): 237.2 [M+1]

Step 3

4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexan-1-formaldehyde **276e**

Compound **276d** (500 mg, 2.12 mmol) was dissolved in DCM(20 mL). Under a nitrogen atmosphere, the mixture was cooled to -75℃, followed by the slow dropwise addition of DIBAL-H (1 M, 6.35 mL), and the mixture was stirred at -75°C to allow for reacting for 1.0 hours. Methanol (3.0 mL) was added dropwise to the reaction mixture, which was further stirred for 1.0 hour, then warmed to room temperature and stirred for 1.0 hour. Sodium sulfate decahydrate (2 g) was added to the reaction mixture, which was then stirred for 0.5 hours and filtered, and the filtrate was concentrated under a reduced pressure to obtain the crude product of title Compound **276e** (300 mg, 1.56 mmol, yield: 73.75%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 192.9 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.23 (s, 1H), 7.05 (s, 1H), 3.78 (s, 3H), 2.58 – 2.49 (m, 1H), 2.41 – 2.36 (m, 1H), 2.11 – 2.06 (m, 2H), 1.82 – 1.76 (m, 2H), 1.69 – 1.64 (m, 2H), 1.44 – 1.38 (m, 2H).

Step 4

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*s*,4*s*)-4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **276-1**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{[(1*r*,4*r*)-4-(1-methyl-1*H*-pyrazol-4-yl)cyclohexyl]methyl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **276-2**

Compound **145d** (160 mg, 375.18 μmol) and Compound **276e**(108.20 mg, 562.78 μmol) were dissolved in methanol (5.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (70.73 mg, 1.13 mmol) was added, and the reaction mixture was stirred at room temperature for 11.0 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added, and the mixture was then extracted with dichloromethane (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 36%-66%), and the obtained mixture was purified by the SFC(separation column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: CO_2-EtOH (0.1% ammonia water), elution gradient: 45%), to obtain the title Compounds **276-1** (9.63 mg, 15.98 μmol, yield: 4.26%) and **276-2** (15.2 mg, 25.22 μmol, yield: 6.72%).

Compound 276-1:

MS m/z (ESI): 603.5[M+1]

SFC: retention time: 1.726 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.87 – 7.74 (m, 1H), 7.65 – 7.50 (m, 1H), 7.41 (s, 1H), 7.37 – 7.16 (m, 3H), 6.85 - 6.60 (m, 1H), 4.59 – 3.99 (m, 1H), 3.83 (s, 3H), 3.79 – 3.46 (m, 5H), 3.45 – 3.33 (m, 1H), 3.28 – 3.18 (m, 2H), 3.17 – 2.83 (m,2H), 2.77 – 2.69 (m, 1H), 2.59 (s, 3H), 2.57 – 2.42 (m, 2H), 2.36 – 1.86 (m, 1H), 1.82 – 1.71 (m, 4H), 1.70 – 1.55 (m, 3H).

Compound 276-2:

MS m/z (ESI): 603.4 [M+1]

SFC: retention time: 2.495 min; Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA); elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.74 (m, 1H), 7.64 – 7.50 (m, 1H), 7.38 – 7.17 (m, 4H), 6.85 – 6.59 (m, 1H),4.65 – 4.01 (m, 2H), 3.87 – 3.72 (m, 6H), 3.64 – 3.54 (m, 1H), 3.41 – 3.33 (m, 1H), 3.29 – 2.76 (m, 4H), 2.60 (s, 3H), 2.53 -2.36 (m, 3H), 2.01 – 1.83 (m, 4H), 1.52 – 1.41 (m, 1H), 1.39 – 1.23 (m, 4H), 1.21 – 1.02 (m, 3H), 0.80 (br d, J = 4.6 Hz, 1H).

Example 280

1-(4-{1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]propyl}piperidin-1-yl)ethan-1-one **280**

Step 1 Step 2 Step 3

Step 1

4-{1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]propyl}piperidin-1-tert-butyl carboxylate **280b**

Compound **145d** (120 mg, 281.39 μmol) and 4-propionylpiperidin-1-tert-butyl formate **280a** (74.70 mg, 309.53 μmol) were dissolved in methanol (3.0 mL), followed by the addition of zinc chloride (76.70 mg, 562.78 μmol), and the mixture was stirred at 55°C for 1.0 hour. Sodium cyanoborohydride (53.05 mg, 844.16 μmol) was added, and the mixture was stirred at 55℃ for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **280b** (180 mg, 276.16 μmol, yield: 98.14%) as yellow oil.
MS m/z (ESI):652.2[M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[1-(piperidin-4-yl)propyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **280c**

Compound **280b** (180 mg, 276.16 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **280c** (150 mg, 271.90 μmol, yield: 98.46%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 552.3 [M+1]

Step 3

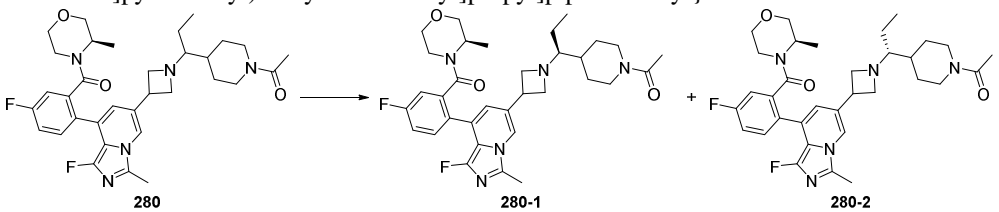
1-(4-{1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]propyl}piperidin-1-yl)ethan-1-one **280**

Triethylamine (82.54 mg, 815.71 μmol) and Compound **280c** (150 mg, 271.90 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetyl chloride (25.61 mg, 326.28 μmol). The reaction mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 25%-55%), to obtain the title Compound **280** (55 mg, 92.64 μmol, yield: 34.07 %) as yellow solid.
MS m/z (ESI): 594.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.79 (m, 1H), 7.62 – 7.49 (m, 1H), 7.44 – 7.23 (m, 2H), 6.87 – 6.43 (m, 1H), 4.50 – 3.38 (m, 9H), 3.23 – 3.04 (m, 3H), 3.02 – 2.60 (m, 3H), 2.55 (s, 3H), 2.43 – 2.29 (m, 1H), 2.06 – 1.99 (m, 1H), 1.99 – 1.94 (m, 3H), 1.71 – 1.44 (m, 3H), 1.34 – 1.01 (m, 6H), 0.91 – 0.84 (m, 3H), 0.79 – 0.52 (m, 1H).

Examples 280-1 and 280-2

1-{4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]propyl]piperidin-1-yl}ethan-1-one **280-1**

1-{4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]propyl]piperidin-1-yl}ethan-1-one **280-2**



Compound **280** (47.77 mg, 80.46 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL DAICEL ChiralPak IF, (250*50 mm, 10 um), mobile phase: n-hexane-ethanol (0.1%isopropylamine); elution gradient: 58%), to obtain the title Compounds **280-1** (14.75 mg, 24.84 μmol, yield: 30.88%) and **280-2** (16.31 mg, 27.47 μmol, yield: 34.14%).

Single-configuration Compound 280-1:

MS m/z (ESI):594.4[M+1]
Chiral HPLC analysis: retention time: 2.226 min; chromatographic column: Chiralpak IF-3 50 x 4.6mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-EtOH (0.05% isopropylamine): elution gradient: 35%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 10.8 Hz, 1H), 7.67 – 7.18 (m, 3H), 6.97 – 6.38 (m, 1H), 4.51 – 3.39

(m, 9H), 3.21 – 3.05 (m, 3H), 3.03 – 2.65 (m, 3H), 2.55 (s, 3H), 2.44 – 2.30 (m, 1H), 2.06 – 1.91 (m, 4H), 1.69 – 1.41 (m, 3H), 1.34 – 1.04 (m, 6H), 0.91 – 0.53 (m, 4H).

Single-configuration Compound 280-2:

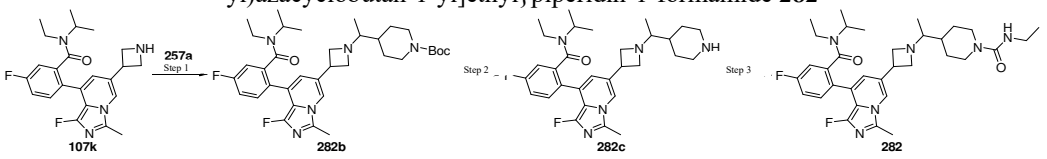
MS m/z (ESI):594.3[M+1]

Chiral HPLC analysis: retention time: 3.682 min; chromatographic column: Chiralpak IF-3 50 x 4.6mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-EtOH (0.05% isopropylamine): elution gradient: 35%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.74 (m, 1H), 7.66 – 7.16 (m, 3H), 6.89 – 6.51 (m, 1H), 4.53 – 3.38 (m, 9H), 3.22 – 3.08 (m, 3H), 3.05 – 2.65 (m, 3H), 2.55 (s, 3H), 2.42 – 2.29 (m, 1H), 2.08 – 1.89 (m, 4H), 1.70 – 1.44 (m, 3H), 1.34 – 1.05 (m, 6H), 0.91 – 0.54 (m, 4H).

Example 282

N-ethyl-4-{1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-formamide **282**



Step 1

4-{1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-tert-butyl carboxylate **282b**

Compound **107k** (158 mg, 383.05 μmol) and 4-acetylpiperidin-1-tert-butyl formate **257a** (95.77 mg, 421.36 μmol) were dissolved in methanol (3.0 mL), followed by the addition of zinc chloride (104.42 mg, 766.11 μmol), and the mixture was stirred at 55°C for 1.0 hour. Sodium cyanoborohydride (72.22 mg, 1.15 mmol) was added, and the mixture was stirred at 55°C for 11 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **282b** (220 mg, 352.69 μmol, yield: 92.07%) as yellow oil.

MS m/z (ESI):624.3 [M+1]

Step 2

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **282c**

Compound **282b** (220 mg, 352.69 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **282c** (180 mg, 343.74 μmol, yield: 97.46%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 524.3 [M+1]

Step 3

N-ethyl-4-{1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-formamide **282**

Triethylamine (52.17 mg, 515.60 μmol) and Compound **282c** (90 mg, 171.87 μmol) were dissolved in dichloromethane (2.0 mL), and cooled to 0°C, followed by the addition of isocyanoethane (18.32 mg, 257.80 μmol). The reaction mixture was stirred at room temperature for 2 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **282** (48 mg, 80.71 μmol, yield: 46.96 %) as yellow solid.

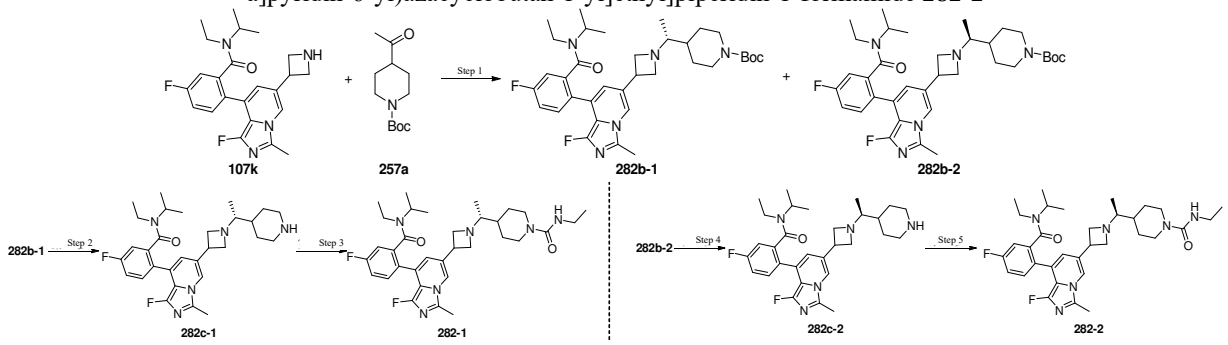
MS m/z (ESI): 595.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.57 – 7.47 (m, 1H), 7.39 – 7.24 (m, 2H), 6.74 – 6.52 (m, 1H), 6.37 – 6.30 (m, 1H), 4.05 – 3.93 (m, 2H), 3.55 – 3.32 (m, 5H), 3.11 – 2.87 (m, 5H), 2.53 (s, 4H), 2.49 – 2.44 (m, 1H), 2.22 – 2.10 (m, 1H), 1.68 – 1.32 (m, 3H), 1.17 – 0.87 (m, 9H), 0.86 – 0.71 (m, 6H), 0.39 (s, 2H).

Examples 282-1 and 282-2

N-ethyl-4-[(1*R*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-formamide **282-1**

N-ethyl-4-[(1*S*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-formamide **282-2**



Step 1

4-[(1*R*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-tert-butyl carboxylate **282b-1**

4-[(1*S*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-tert-butyl carboxylate **282b-2**

Compound **107k** (800 mg, 1.94 mmol) and 4-acetylpiperidin-1-tert-butyl formate **257a** (529.02 mg, 2.33 mmol) were dissolved in methanol (20 mL), followed by the addition of zinc chloride (793.04 mg, 5.82 mmol), and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (365.65 mg, 5.82 mmol) was added, and the mixture was stirred at 50°C for 11 hours. A saturated aqueous sodium carbonate solution (50 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude compound was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IG (250 mm * 30 mm,10 um), mobile phase: CO_2-ethanol (0.1% ammonia water); elution gradient: 33%), to obtain the title Compounds **282b-1** (447 mg, 716.61 μmol, yield: 36.95%) and **282b-2** (502 mg, 804.78 μmol, yield: 41.49%).

Single-configuration Compound 282b-1:

MS m/z (ESI):624.3[M+1]

Chiral SFC analysis: retention time: 2.019 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 282b-2:

MS m/z (ESI):624.4 [M+1]

Chiral SFC analysis: retention time: 1.927 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Step 2

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*)-1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **282c-1**

Compound **282b-1** (447 mg, 716.61 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed once with saturated brine (50 mL), then dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **282c-1** (344 mg, 656.92 μmol, yield: 91.67%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 524.2 [M+1]

Step 3

N-ethyl-4-[(1*R*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-formamide **282-1**

Triethylamine (49.28 mg, 486.96 μmol) and Compound **282c-1** (85 mg, 162.32 μmol) were dissolved in dichloromethane (5.0 mL), and cooled to 5°C, followed by the addition of isocyanoethane (13.84 mg, 194.78 μmol). The reaction mixture was stirred at room temperature for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL×3). The organic phase was dried over anhydrous sodium

sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **282-1** (48.96 mg, 82.32 μmol, yield: 50.72%) as yellow solid.
MS m/z (ESI): 595.4 [M+1]
Chiral SFC analysis: retention time: 1.285 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.82 – 7.73 (m, 1H), 7.60 – 7.50 (m, 1H), 7.35 – 7.25 (m, 1H), 7.25 – 7.16 (m, 1H), 6.79 – 6.67 (m, 1H), 4.59 (s, 1H), 4.07 (t, J = 10.6 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H), 3.66 – 3.54 (m, 2H), 3.52 – 3.37 (m, 1H), 3.28 – 3.13 (m, 4H), 3.10 – 2.97 (m, 1H), 2.78 – 2.63 (m, 2H), 2.58 (s, 3H), 2.43 – 2.31 (m, 1H), 1.71 – 1.60 (m, 2H), 1.52 (t, J = 14.4 Hz, 1H), 1.36 – 1.12 (m, 3H), 1.10 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 6.4 Hz, 2H), 0.96 – 0.83 (m, 6H), 0.43 (d, J = 4.4 Hz, 2H)..

Step 4

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*S*)-1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **282c-2**

Compound **282b-2** (502 mg, 804.78 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, washed once with saturated brine (50 mL), then dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **282c-2** (404 mg, 771.49 μmol, yield: 95.86%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 524.2 [M+1]

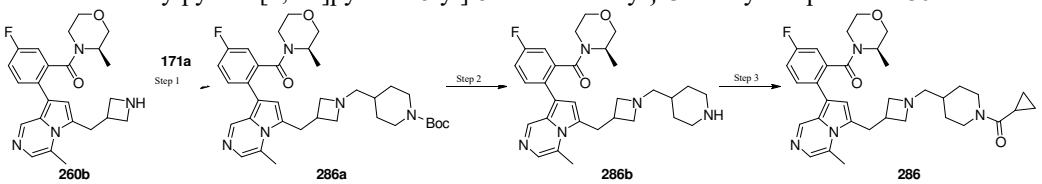
Step 5

N-ethyl-4-[(1*S*)-1-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-formamide **282-2**

Triethylamine (57.97 mg, 572.89 μmol) and Compound **282c-2** (100 mg, 190.96 μmol) were dissolved in dichloromethane (5.0 mL), and cooled to 5°C, followed by the addition of isocyanoethane (11.88 mg, 151.40 μmol). The reaction mixture was stirred at room temperature for 2 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **282-2** (27.31 mg, 45.92 μmol, yield: 24.05 %) as yellow solid.
MS m/z (ESI): 595.3 [M+1]
Chiral SFC analysis: retention time: 1.280 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 – 7.79 (m, 1H), 7.58 – 7.48 (m, 1H), 7.41 – 7.25 (m, 2H), 6.75 – 6.56 (m, 1H), 6.35 (t,J = 5.2 Hz, 1H), 4.30 – 3.95 (m, 2H), 3.56 – 3.41 (m, 4H), 3.13 – 2.66 (m, 6H), 2.54 (s, 3H), 2.47 – 2.32 (m, 1H), 2.21 – 2.12(m, 1H), 1.69 – 1.32 (m, 3H), 1.17 – 0.65 (m, 16H), 0.40 (br s, 2H).

Example 286

(3*R*)-4-{2-[6-({1-[(1-cyclopropane carbonylpiperidin-4-yl)methyl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **286**



Step 1

4-({3-[(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl]azacyclobutan-1-yl}methyl)piperidin-1-tert-butyl carboxylate **286a**

Compound **260b** (350 mg, 652.36 μmol, trifluoroacetate) and Compound **171a** (166.96 mg, 782.83 μmol) were dissolved in methanol (10 mL). Triethylamine (132.02 mg, 1.30 mmol) was added, and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (122.99 mg, 1.96 mmol) was added, and the reaction mixture was stirred at room temperature for 12.0 hour. A saturated aqueous sodium bicarbonate solution (20 mL) was added, and the mixture was then extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified

by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **286a** (380 mg, 613.13 μmol, yield: 93.99%) as yellow solid.
MS m/z (ESI): 620.5[M+1]

Step 2

(3*R*)-4-{5-fluoro-2-[4-methyl-6-({1-[(piperidin-4-yl)methyl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]benzoyl}-3-methylmorpholine **286b**

Compound **286a** (120 mg, 193.62 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **286b** (100 mg, 192.44 μmol, yield: 99.39). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 520.1 [M+1]

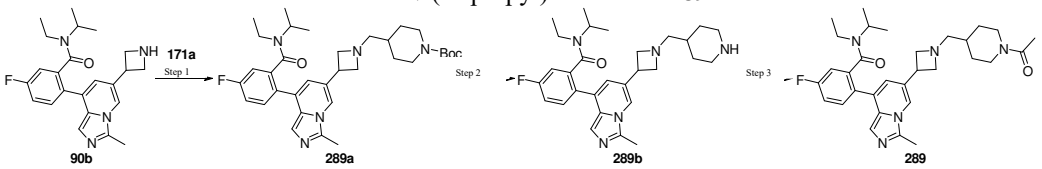
Step 3

(3*R*)-4-{2-[6-({1-[(1-cyclopropane carbonylpiperidin-4-yl)methyl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **286**

Cyclopropanecarboxylic acid (20.87 mg, 242.47 μmol), triethylamine (47.91 mg, 473.43 μmol) and HATU(92.19 mg, 242.47 μmol) were dissolved in dichloromethane (2.0 mL), and stirred at room temperature for 10 min, followed by the addition of Compound **286b** (105 mg, 202.06 μmol). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 22%-52%), to obtain the title Compound **286** (51.71 mg, 87.98 μmol, yield: 43.54%) as yellow solid.
MS m/z (ESI): 588.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 – 8.38 (m, 1H), 7.63 – 7.45 (m, 1H), 7.39 – 7.18 (m, 3H), 6.63 – 6.51 (m, 1H), 4.37 – 3.90 (m, 3H), 3.86 – 3.36 (m, 7H), 3.23 – 2.88 (m, 3H), 2.86 – 2.70 (m, 7H), 2.30 – 2.22 (m, 2H), 1.96 – 1.87 (m, 1H), 1.81 – 1.43 (m, 4H), 1.25 – 0.85 (m, 4H), 0.71 – 0.28 (m, 5H).

Example 289

2-(6-{1-[(1-acetylpiperidin-4-yl)methyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **289**



Step 1

4-{[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]methyl}piperidin-1-tert-butyl carboxylate **289a**

Compound **90b** (398 mg, 1.01 mmol) and 4-acetylpiperidin-1-tert-butyl formate **171a** (258.21 mg, 1.21 mmol) were dissolved in methanol (10.0 mL), followed by the addition of zinc chloride (109.18 mg, 801.05 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (190.21 mg, 3.03 mmol) was added, and the mixture was stirred at 25℃ for 11 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product of title Compound **289b** (580 mg, 980.13 μmol, yield: 97.04%) was obtained as yellow oil.
MS m/z (ESI):592.2[M+1]

Step 2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(piperidin-4-yl)methyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **289b**

Compound **289a** (580 mg, 980.13 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 g, 8.77 mmol, 675.68 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **289b** (470 mg, 955.98 μmol, yield: 97.54%).The crude product was directly used in the next step of

reaction without purification.
MS m/z (ESI): 492.2 [M+1]

Step 3

2-(6-{1-[(1-acetylpiperidin-4-yl)methyl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **289**

Triethylamine (49.40 mg, 488.16 μmol) and Compound **289b** (80 mg, 162.72 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetyl chloride (15.33 mg, 195.26 μmol). The reaction mixture was stirred at room temperature for 12 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 22%-52%), to obtain the title Compound **289** (26.35 mg, 49.37 μmol, yield: 30.34 %) as yellow solid.
MS m/z (ESI): 534.4 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.40 (m, 2H), 7.23 – 7.01 (m, 3H), 6.96 – 6.74 (m, 1H), 4.65 – 4.39 (m, 1H),3.85 – 3.28 (m, 6H), 3.24 – 2.78 (m, 4H), 2.67 (s, 3H), 2.58 – 2.33 (m, 3H), 2.08 (s, 3H), 1.89 – 1.79 (m, 1H), 1.62 – 1.47 (m,1H), 1.31 – 0.63 (m, 10H), 0.25 (m, 2H).

Examples 291 and 291-1

(3*r*,4*r*)-1-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-4-methoxypyrrolidin-3-ol **291**

(3*R*,4*R*)-1-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-4-methoxypyrrolidin-3-ol **291-1**

Step 1 Step 2

Step 1

(3*r*,4*r*)-1-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-4-methoxypyrrolidin-3-ol **291**

Compound **199b-1** (220 mg, 408.45 μmol) and (3*r*,4*r*)-4-methoxypyrrolidin-3-ol (94.11 mg, 612.67 μmol, hydrochloride) were dissolved in methanol (5.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (77.00 mg, 1.23 mmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title product **291** (13.54 mg, 21.16 μmol, yield: 5.18%) as yellow solid.
MS m/z (ESI):640.5 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.34 (m, 2H), 7.26 – 7.06 (m, 2H), 6.84 – 6.55 (m, 1H), 4.66 – 4.03 (m, 2H),3.94 – 3.43 (m, 6H), 3.38 (s, 3H), 3.33 – 2.66 (m, 8H), 2.63 (s, 3H), 2.53 – 1.88 (m, 6H), 1.71 – 1.06 (m, 7H), 0.99 – 0.56 (m,7H).

Step 2

(3*R*,4*R*)-1-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-4-methoxypyrrolidin-3-ol **291-1**

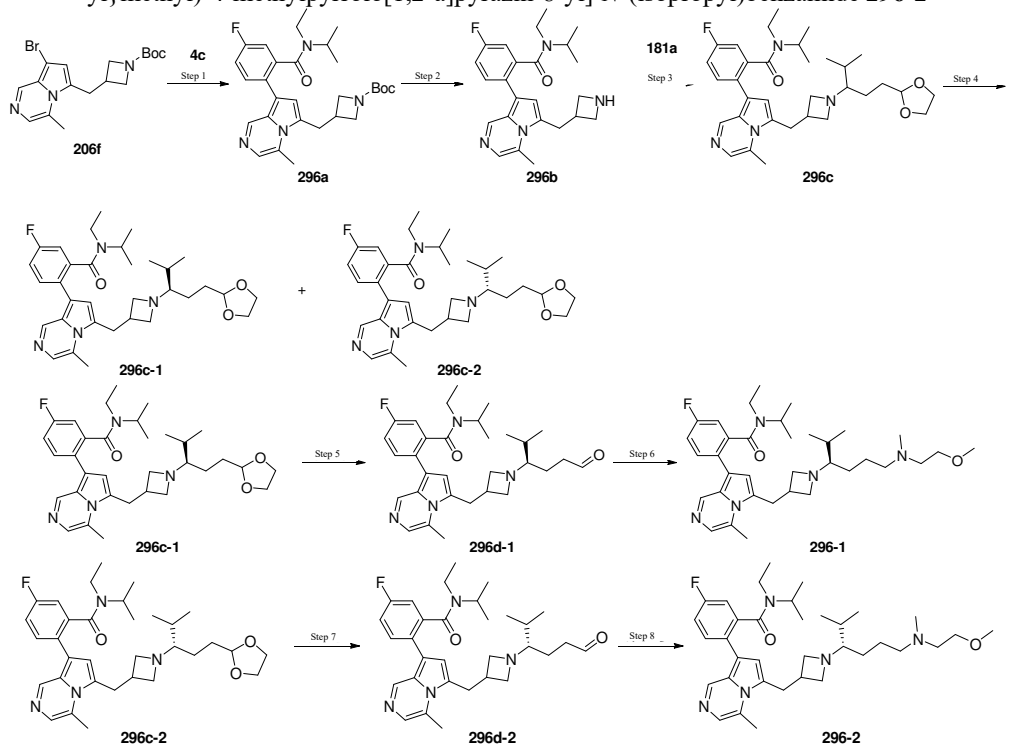
Compound **291** (130 mg, 203.20 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), mobile phase: acetonitrile, water (0.1% ammonia water); elution gradient: 30%), and the resulting crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 13%-43%), to obtain the title product **291-1** (5.65 mg, 8.83 μmol, yield: 4.35%) as yellow solid.
MS m/z (ESI):640.5 [M+1]
Chiral SFC analysis: retention time: 1.433 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.86 – 7.74 (m, 1H), 7.64 – 7.50 (m, 1H), 7.41 – 7.15 (m, 2H), 6.89 – 6.56 (m,

1H),4.79 – 4.09 (m, 3H), 4.08 – 3.38 (m, 7H), 3.34 (s, 3H), 3.28 – 2.62 (m, 7H), 2.60 (s, 3H), 2.52 – 2.17 (m, 4H), 1.93 – 0.51 (m,15H).

Examples 296-1 and 296-2

N-ethyl-5-fluoro-2-[6-({1-[(3*R*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **296-1**

N-ethyl-5-fluoro-2-[6-({1-[(3*S*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **296-2**



Step 1

3-[(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **296a**

Compound **206f** (300 mg, 788.90 μmol), Compound **4c**(396.68 mg, 1.18 mmol) and potassium phosphate (502.37 mg, 2.37 mmol) were dissolved in dioxane (12 mL) and water (3.0 mL). Pd(dtbpf)Cl_2 (51.42 mg, 78.89 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **296a** (300 mg, 589.82 μmol, yield: 74.77%) as yellow solid.

MS m/z (ESI): 509.1 [M+1]

Step 2

2-{6-[(azacyclobutan-3-yl)methyl]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **296b**

Compound **296a** (300 mg, 590.97 μmol) was dissolved in methane dioxide (6.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, then dissolved by adding DCM (5.0 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **296b** (240 mg, 587.50 μmol, yield: 99.41). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.2 [M+1]

Step 3

2-[6-({1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-

yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **296c**

Compound **296b** (240 mg, 587.50 μmol) and Compound **181a** (121.42 mg, 705.00 μmol) were dissolved in methanol (4.0 mL). Zinc chloride (240.22 mg, 1.76 mmol) was added, and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (110.76 mg, 1.76 mmol) and stirring at 50°C for 12.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 43%-73%), to obtain the title Compound **296c** (220 mg, 389.57 μmol, yield: 66.31%) as yellow solid.

MS m/z (ESI): 565.5[M+1]

Step 4

2-[6-({1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **296c-1**

2-[6-({1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **296c-2**

Compound **296c** (220 mg, 389.57 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: CO_2-MeOH (0.1% ammonia water); elution gradient: 20%), to obtain the title Compounds **296c-1** (83 mg, 146.97 μmol, yield: 37.73%) and **296c-2** (87 mg, 154.06 μmol, yield: 39.55%).

Single-configuration Compound 296c-1:

MS m/z (ESI):565.5 [M+1]

Chiral HPLC analysis: retention time: 1.975 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 296c-2:

MS m/z (ESI):565.6 [M+1]

Chiral HPLC analysis: retention time: 1.294 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Step 5

N-ethyl-5-fluoro-2-[4-methyl-6-({1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8yl]-*N*-(isopropyl)benzamide **296d-1**

Compound **296c-1** (83 mg, 146.97 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with a saturated aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **296d-1** (70 mg, 134.44 μmol, yield: 91.47%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 296d-1:

MS m/z (ESI): 521.2 [M+1]

Step 6

N-ethyl-5-fluoro-2-[6-({1-[(3*R*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **296-1**

The crude product of Compound **296d-1** (70 mg, 134.44 μmol) and 2-methoxy-*N*-methylethylamine (23.97 mg, 268.88 μmol) were dissolved in methanol (2 mL), followed by the addition of acetic acid (8.07 mg, 134.44 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (25.35 mg, 403.32 μmol) was added, allowing for reacting at room temperature for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 35%-65%). The title Compound **296-1** (38.69 mg, 65.15 μmol, yield: 48.46%) was obtained.

Single-configuration Compound 296-1:

MS m/z (ESI):594.3 [M+1]

Chiral SFC: retention time: 0.766 min; chromatographic column: Chiralcel OJ-3 50 × 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 8.60 – 8.52 (m, 1H), 7.60 – 7.52 (m, 1H), 7.37 – 7.14 (m, 3H), 6.82 – 6.73 (m, 1H),

4.71 – 4.27 (m, 2H), 3.70 – 3.49 (m, 7H), 3.18 – 2.99 (m, 3H), 2.87 – 2.84 (m, 3H), 2.67 – 2.58 (m, 2H), 2.48 – 2.39 (m, 2H), 2.33 – 2.28 (m, 3H), 2.22 – 2.03 (m, 1H), 1.90 – 1.81 (m, 1H), 1.61 – 1.52 (m, 2H), 1.41 – 1.16 (m, 5H), 1.03 – 0.80 (m, 13H), 0.36 – 0.32 (m, 2H).

Step 7

N-ethyl-5-fluoro-2-[4-methyl-6-({1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8yl]-*N*-(isopropyl)benzamide **296d-2**

Compound **296c-2** (87 mg, 154.06 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with a saturated aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **296d-2** (75 mg, 144.04 μmol, yield: 93.50%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 296d-2:

MS m/z (ESI): 521.2 [M+1]

Step 8

N-ethyl-5-fluoro-2-[6-({1-[(3*S*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **296-2**

The crude product of Compound **296d-2** (75 mg, 144.04 μmol) and 2-methoxy-*N*-methylethylamine (25.68 mg, 288.09 μmol) were dissolved in methanol (2 mL), followed by the addition of acetic acid (8.65 mg, 144.04 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (27.16 mg, 432.13 μmol) was added, allowing for reacting at room temperature for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 35%-65%). The title Compound **296-2** (33.45 mg, 56.33 μmol, yield: 39.11%) was obtained.

Single-configuration Compound 296-2:

MS m/z (ESI):594.4 [M+1]

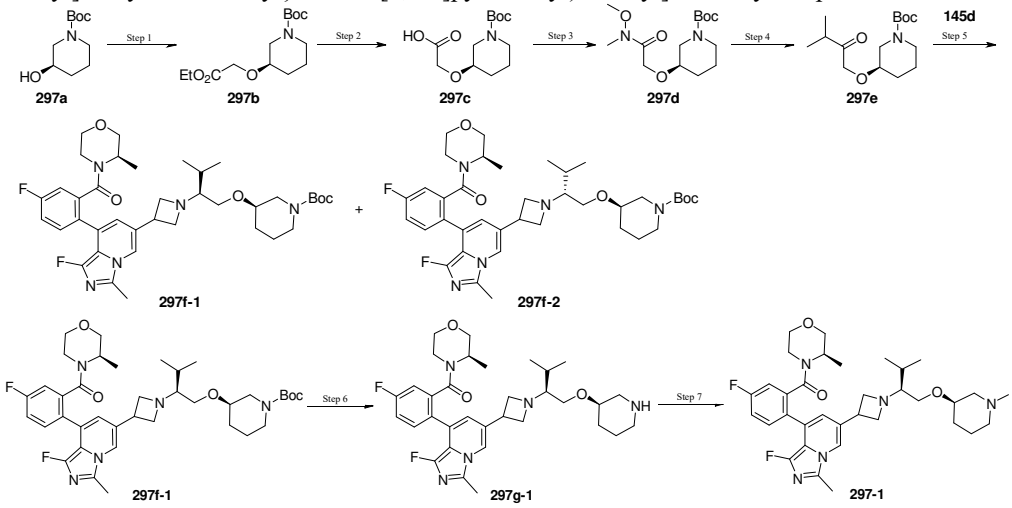
Chiral SFC: retention time: 1.177 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

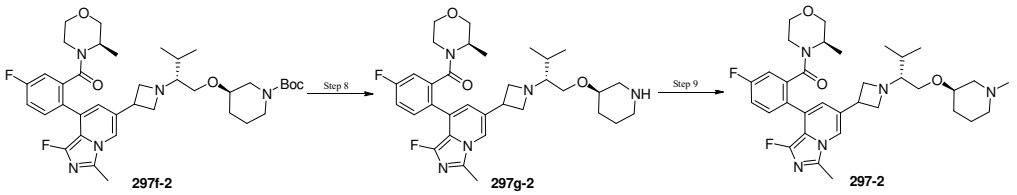
^{1}H NMR (400 MHz, CD_3OD) δ 8.55 – 8.52 (m, 1H), 7.60 – 7.49 (m, 1H), 7.35 – 7.13 (m, 3H), 6.77 – 6.72 (m, 1H), 4.64 – 4.32 (m, 2H), 3.67 – 3.48 (m, 7H), 3.14 – 2.98 (m, 3H), 2.85 – 2.82 (m, 3H), 2.64 – 2.58 (m, 2H), 2.45 – 2.38 (m, 2H), 2.31 – 2.25 (m, 3H), 2.19 – 2.04 (m, 1H), 1.88 – 1.79 (m, 1H), 1.60 – 1.49 (m, 2H), 1.35 – 1.15 (m, 5H), 1.00 – 0.78 (m, 13H), 0.34 – 0.30 (m, 2H).

Examples 297-1 and 297-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*R*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-{[(3*R*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297-2**





Step 1

(3*R*)-3-(2-ethoxy-2-oxoethoxy)piperidin-1-tert-butyl carboxylate **297b**

(3*R*)-3-hydroxylpiperidin-1-tert-butyl carboxylate **297a** (5 g, 24.84 mmol) was dissolved in THF (70 mL), and cooled to 0°C, followed by the addition of sodium hydride (1.19 g, 29.81 mmol, 60% purity), and the mixture was stirred for 0.5 hours. 2-Bromoethyl acetate (4.98 g, 29.81 mmol) was added dropwise, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was cooled to 0℃, followed by the addition of a saturated aqueous ammonium chloride solution (50 mL), and the reaction mixture was extracted with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **297b** (2 g, 6.96 mmol, yield: 28.02%).

MS m/z (ESI): 232.1 [M-55]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.04 (m, 4H), 3.82 (s, 1H), 3.65 – 3.56 (m, 1H), 3.41 (tt, J = 3.9, 8.1 Hz, 1H), 3.04 (br s, 2H), 1.99 (br d, J = 5.5 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.64 – 1.53 (m, 1H), 1.49 – 1.44 (m, 10H), 1.26 (br s, 3H).

Step 2

2-{[(3*R*)-1-[(tert-butoxy)carbonyl]piperidin-3-yl]oxy}acetic acid **297c**

Under the protection of nitrogen, Compound **297b** (1.8 g, 6.26 mmol) was dissolved in ethanol (8.0 mL) and water (8.0 mL), followed by the addition of lithium hydroxide (1.31 g, 31.32 mmol), and the reaction mixture was stirred at room temperature for 12 hours. A 1M aqueous hydrochloric acid solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **297c** (1.16 g, 4.47 mmol, yield: 71.42%).

MS m/z (ESI): 204.1 [M-55]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (br s, 1H), 3.97 (d, J = 10.6 Hz, 2H), 3.75 – 3.49 (m, 1H), 3.37 (tt, J = 3.5, 7.0 Hz, 2H), 1.82 (br d, J = 4.5 Hz, 1H), 1.70 – 1.56 (m, 1H), 1.54 – 1.22 (m, 13H).

Step 3

(3*R*)-3-{[methoxy(methyl)aminoformyl]methoxy}piperidin-1-tert-butyl carboxylate **297d**

Compound **297c** (1.16 g, 4.47 mmol) was dissolved in DCM (30 mL), followed by the addition of HATU (2.04 g, 5.37 mmol), triethylamine (1.36 g, 13.42 mmol) and *N*-methoxymethylamine (523.65 mg, 5.37 mmol, hydrochloride). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium carbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **297d** (1 g, 3.31 mmol, yield: 73.93%).

MS m/z (ESI): 303.1 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 – 4.22 (m, 2H), 3.99 – 3.56 (m, 5H), 3.45 (tt, J = 3.8, 8.2 Hz, 1H), 3.25 – 2.94 (m, 5H), 2.03 (br d, J = 12.0 Hz, 1H), 1.67 – 1.54 (m, 1H), 1.45 (s, 11H).

Step 4

(3R)-3-(3-methyl-2-oxobutoxy)piperidin-1-tert-butyl carboxylate **297e**

Under the protection of nitrogen, Compound **297d** (500 mg, 1.65 mmol) was dissolved in tetrahydrofuran (10 mL), and cooled to -70℃. An isopropyllithium solution (1.0 M, 5.60 mL) was added dropwise to the reaction mixture, after which the reaction mixture was stirred at -70℃ for 3.0 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (15 mL) at low temperature, and extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **297e** (160 mg, 560.66 μmol, yield: 33.90%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 – 4.09 (m, 2H), 3.72 (br s, 1H), 3.58 – 3.47 (m, 1H), 3.35 (br dd, J = 3.5, 7.0 Hz, 1H), 3.17 (br d, J = 1.3 Hz, 2H), 2.82 (br s, 1H), 2.02 – 1.86 (m, 1H), 1.78 (ddd, J = 3.0, 6.6, 10.0 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.46 (s, 10H), 1.11 (d, J = 6.8 Hz, 6H).

Step 5

(3*R*)-3-[(2*S*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-

a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]piperidin-1-tert-butyl carboxylate **297f-1**
(3*R*)-3-[(2*R*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]piperidin-1-tert-butyl carboxylate **297f-2**

Compound **145d** (125 mg, 293.11 μmol) and Compound **297e** (92.01 mg, 322.42 μmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (79.90 mg, 586.22 μmol), and the mixture was stirred at 50℃ for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (55.26 mg, 879.34 μmol), allowing for reacting at 50℃ for 10 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the resulting solid was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IG (250 mm * 30 mm,10 um), mobile phase: CO_2-[ACN/EtOH (0.1% ammonia water)]; elution gradient: 25%), to obtain the title Compounds **297f-1** (40 mg, 57.48 μmol, yield: 19.6%) and **297f-2** (40 mg, 57.48 μmol, yield: 19.6%).

Single-configuration Compound 297f-1:

MS m/z (ESI):696.1 [M+1]

Chiral HPLC analysis: retention time: 1.643 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 297f-2:

MS m/z (ESI):696.2 [M+1]

Chiral HPLC analysis: retention time: 1.789 min; chromatographic column: Chiralpak IG-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% DEA): elution gradient: 5%-40%.

Step 6

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-[(3*R*)-piperidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297g-1**

Compound **297f-1** (40.00 mg, 57.48 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product of title Compound **297g-1** (35 mg, 58.75 μmol, yield: 102.21%) was obtained as yellow solid. The crude product was directly used in the next step of reaction without treatment.

Step 7

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*R*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297-1**

Compound **297g-1** (40.00 mg, 56.36 μmol, trifluoroacetate) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (8.55 mg, 84.54 μmol) and formaldehyde (23.50 mg, 281.79 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (10.62 mg, 169.07 μmol) was added, allowing for reacting at 25℃ for 1.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 40%-70%), to obtain the title Compound **297-1** (12.56 mg, 20.60 μmol, yield: 36.55%).

Single-configuration Compound 297-1:

MS m/z (ESI):610.4 [M+1]

Chiral SFC analysis: retention time: 1.123 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.73 (m, 1H), 7.63 – 7.23 (m, 3H), 6.83 – 6.44 (m, 1H), 4.44 – 3.34 (m, 8H), 3.30 – 2.53 (m, 12H), 2.28 – 2.18 (m, 1H), 2.11 (s, 3H), 1.90 – 1.53 (m, 5H), 1.43 – 1.30 (m, 1H), 1.22 – 0.70 (m, 10H).

Step 8

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-[(3*R*)-piperidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297g-2**

Compound **297f-2** (40 mg, 57.48 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product of title Compound **297g-2** (35 mg, 58.75 μmol, yield: 102.21%) was obtained as yellow solid. The crude product was directly used in the next step of reaction without treatment.

Step 9

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-{[(3*R*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **297-2**

Compound **297g-2** (40.00 mg, 56.36 μmol, trifluoroacetate) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (8.55 mg, 84.54 μmol) and formaldehyde (23.50 mg, 281.79 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (10.62 mg, 169.07 μmol) was added, allowing for reacting at 25°C for 1.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 40%-70%), to obtain the title Compound **297-2** (8.93 mg, 14.65 μmol, yield: 25.99%).

Single-configuration Compound 297-2:

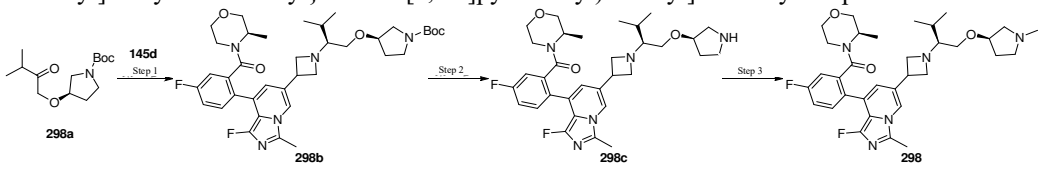
MS m/z (ESI):610.4 [M+1]

Chiral SFC: retention time: 1.135 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz,DMSO-d_6) δ 7.94 – 7.76 (m, 1H), 7.63 – 7.22 (m, 3H), 6.82 – 6.42 (m, 1H), 4.43 – 3.41 (m, 8H), 3.24 – 2.53 (m, 12H), 2.28 – 2.21 (m, 1H), 2.12 (s, 3H), 1.87 – 1.55 (m, 5H), 1.43 – 1.31 (m, 1H), 1.21 – 0.74 (m, 10H).

Example 298

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*R*)-1-methylpyrrolidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **298**



Step 1

(3*R*)-3-[(2*S*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]pyrrolidin-1-tert-butyl carboxylate **298b**

Compound **145d** (125 mg, 293.11 μmol) and (3R)-3-(3-methyl-2-oxobutoxy)pyrrolidin-1-tert-butyl carboxylate **298a** (79.54 mg, 293.11 μmol, prepared according to the synthesis route of Compound **297e** by using (3*R*)-3-hydroxylpyrrolidin-1-tert-butyl carboxylate to replace (3*R*)-3-hydroxylpiperidin-1-tert-butyl carboxylate in the first step) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (79.90 mg, 586.22 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (55.26 mg, 879.34 μmol), allowing for reacting at 50°C for 10 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **298b** (110 mg, 161.34 μmol, yield: 55.04%) as colorless oil.

MS m/z (ESI):682.3 [M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-[(3*R*)-pyrrolidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **298c**

Compound **298b** (110 mg, 161.34 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product of title Compound **298c** (110 mg) was obtained. The crude product was directly used in the next step of reaction without treatment.

MS m/z (ESI):582.3 [M+1]

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*R*)-1-methylpyrrolidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **298**

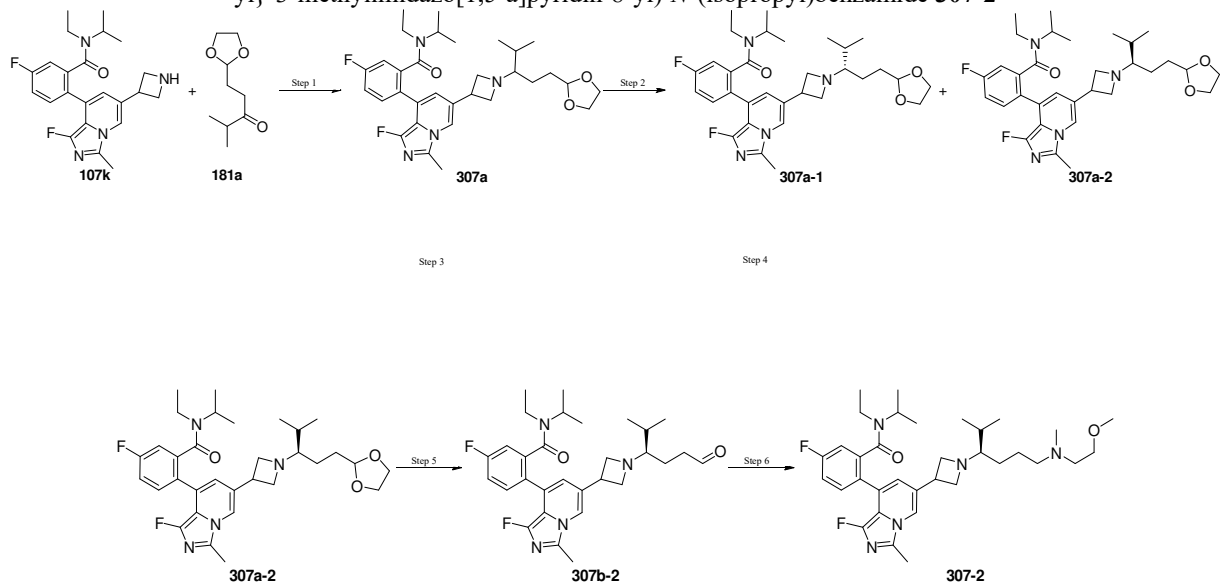
The crude product of Compound **298c** (110 mg) was dissolved in methanol (3.0 mL), followed by the addition of triethylamine (24.00 mg, 237.17 μmol) and formaldehyde (64.15 mg, 790.55 μmol, 37%purity), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (29.81 mg, 474.33 μmol) was added, allowing for reacting at

25℃ for 1.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 44%-74%), to obtain the title Compound **298** (21.26 mg, 35.69 μmol, yield: 22.57%).
MS m/z (ESI):596.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.70 (m, 1H), 7.66 – 7.51 (m, 1H), 7.40 – 7.16 (m, 2H), 6.89 – 6.57 (m, 1H), 4.59 – 3.97 (m, 2H), 3.81 – 3.34 (m, 8H), 3.29 – 2.40 (m, 12H), 2.33 (s, 3H), 2.15 – 2.04 (m, 1H), 1.93 – 1.75 (m, 2H), 1.45 – 0.39 (m, 10H).

Examples 307-1 and 307-2

N-ethyl-5-fluoro-2-(1-fluoro-6-{1-[(3*S*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307-1**

N-ethyl-5-fluoro-2-(1-fluoro-6-{1-[(3*R*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307-2**



Step 1

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **307a**

Compound **107k** (281.64 mg, 682.81 μmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (141.11 mg, 819.37 μmol) were dissolved in methanol (25 mL), followed by the addition of $ZnCl_2$ (279.19 mg, 2.05 mmol), and the mixture was stirred at 25°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (128.73 mg, 2.05 mmol) and stirring at 25℃ for 12 hour. A saturated aqueous sodium carbonate solution (50 mL) was added to the reaction mixture, which was then stirred for 30 min and extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **307a** (350 mg, 615.44 μmol, yield: 90.13%)
MS m/z (ESI): 569.4 [M+1]

Step 2

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **307a-1**

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **307a-2**

Compound **307a** (1.1 g, 1.93 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 50 mm,10 um), mobile phase: n-hexane-isopropanol (0.1%isopropylamine); elution gradient: 10%), to obtain the title Compounds **307a-1** (550 mg, 967.12 μmol, yield: 50.0%) and **307a-2** (500 mg, 879.20 μmol, yield: 45.45%).

Single-configuration Compound 307a-1:

MS m/z (ESI):569.3 [M+1]
Chiral HPLC analysis: retention time: 2.051 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-isopropanol (0.05% isopropylamine): elution gradient: 8%.
Single-configuration Compound 307a-2:
MS m/z (ESI):569.3 [M+1]
Chiral HPLC analysis: retention time: 5.181 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane (0.05% isopropylamine)-isopropanol (0.05% isopropylamine): elution gradient: 8%.

Step 3

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307b-1**

Compound **307a-1** (300.00 mg, 527.52 μmol) was dissolved in acetonitrile (10.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 10.0 mL). The mixture was stirred at 50°C to allow for reacting for 3.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL) and regulating to pH ≥ 7 with a 10 % aqueous NaOH solution, and the reaction mixture was extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **307b-1** (276 mg, 526.07 μmol,yield: 99.72%). The crude product was directly used in the next step of reaction without purification.
Single-configuration Compound 307b-1:
MS m/z (ESI): 525.4 [M+1]

Step 4

N-ethyl-5-fluoro-2-(1-fluoro-6-{1-[(3*S*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307-1**

The crude product of Compound **307b-1** (110.00 mg, 209.67 μmol) and 2-methoxy-*N*-methyl-ethylamine (28.03 mg, 314.50 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (12.59 mg, 209.67 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (39.53 mg, 629.00 μmol) was added, allowing for reacting at 25°C for 12.0 hours under the protection of nitrogen. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 56%-86%). The title Compound **307-1** (11.96 mg, 20.01 μmol, yield: 9.54%) was obtained.
Single-configuration Compound 307-1:
MS m/z (ESI):598.5 [M+1]
Chiral SFC: retention time: 1.177 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.59 – 7.51 (m, 1H), 7.30 (dt, J = 2.8, 8.8 Hz, 1H), 7.24 – 7.16 (m, 1H), 6.79 – 6.70 (m, 1H), 3.80 – 3.72 (m, 1H), 3.71 – 3.65 (m, 1H), 3.65 – 3.53 (m, 2H), 3.53 – 3.41 (m, 3H), 3.34 – 3.31 (m, 2H), 3.31 – 3.29 (m, 2H), 3.29 – 3.18 (m, 2H), 3.09 – 2.98 (m, 1H), 2.63 – 2.54 (m, 5H), 2.41 (q, J = 7.2 Hz, 2H), 2.30 – 2.20 (m, 4H), 1.92 – 1.78 (m, 1H), 1.64 – 1.48 (m, 2H), 1.41 – 1.21 (m, 2H), 1.00 (br d, J = 6.4 Hz, 2H), 0.97 – 0.81 (m, 10H), 0.43 (d, J = 4.4 Hz, 2H).

Step 5

N-ethyl-5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307b-2**

Compound **307a-2** (300.00 mg, 527.52 μmol) was dissolved in acetonitrile (10.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 10.0 mL). The mixture was stirred at 50°C to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL) and regulating to pH ≥ 7 with a 10 % aqueous NaOH solution, and the reaction mixture was extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **307b-2** (276 mg, 526.07 μmol, yield: 99.72%). The crude product was directly used in the next step of reaction without purification.
Single-configuration Compound 307b-2:
MS m/z (ESI): 525.4 [M+1]

Step 6

N-ethyl-5-fluoro-2-(1-fluoro-6-{1-[(3*R*)-6-[(2-methoxyethyl)(methyl)amino]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **307-2**

The crude product of Compound **307b-2** (110.00 mg, 209.67 μmol) and 2-methoxy-*N*-methyl-ethylamine (28.03 mg, 314.50 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (12.59 mg, 209.67 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (39.53 mg, 629.00 μmol)

was added, allowing for reacting at 25℃ for 12.0 hours under the protection of nitrogen. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 44%-74%). The title Compound **307-2** (3.91 mg, 6.54 μmol, yield: 3.12%) was obtained.

Single-configuration Compound 307-2:

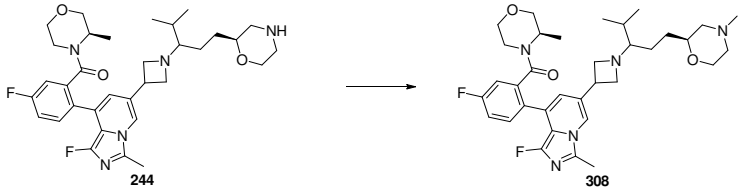
MS m/z (ESI):598.4 [M+1]

Chiral SFC: retention time: 0.771 min; chromatographic column: Chiralcel AS-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.81 – 7.72 (m, 1H), 7.60 – 7.51 (m, 1H), 7.30 (dt, J = 2.4, 8.4 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.82 – 6.65 (m, 1H), 3.79 – 3.72 (m, 1H), 3.72 – 3.66 (m, 1H), 3.65 – 3.54 (m, 2H), 3.54 – 3.38 (m, 3H), 3.32 (d, J = 2.4 Hz, 2H), 3.31 – 3.29 (m, 2H), 3.29 – 3.17 (m, 2H), 3.04 (qd, J = 6.8, 14.0 Hz, 1H), 2.67 – 2.52 (m, 5H), 2.41 (q, J = 7.2 Hz, 2H), 2.31 – 2.16 (m, 4H), 1.92 – 1.79 (m, 1H), 1.65 – 1.50 (m, 2H), 1.44 – 1.33 (m, 1H), 1.31 – 1.21 (m, 1H), 1.00 (d, J = 6.4 Hz, 2H), 0.97 – 0.79 (m, 10H), 0.43 (d, J = 4.8 Hz, 2H).

Example 308

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(2*S*)-4-methylmorpholin-2-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8yl]benzoyl}-3-methylmorpholine **308**



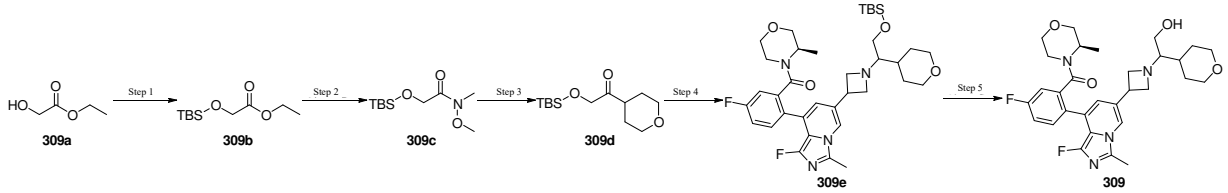
Compound **244** (90 mg, 151.08 μmol) was dissolved in methanol (5.0 mL), followed by the addition of triethylamine (30.57 mg, 302.15 μmol) and formaldehyde (14.71 mg, 181.29 μmol), and the mixture was stirred at 25°C for 10 min. Sodium cyanoborohydride (28.48 mg, 453.23 μmol) was added, allowing for reacting at 25℃ for 12.0 hours under the protection of nitrogen. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%), to obtain the title Compound **308** (5.28 mg, 8.66 μmol, yield: 5.73%).

MS m/z (ESI):610.5 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.73 (m, 1H), 7.66 – 7.50 (m, 1H), 7.39 – 7.12 (m, 2H), 6.87 – 6.53 (m, 1H), 4.59 (s, 6H), 3.84 (d, J = 10.0 Hz, 1H), 3.79 – 3.74 (m, 1H), 3.73 – 3.68 (m, 1H), 3.67 – 3.55 (m, 3H), 3.46 – 3.38 (m, 1H), 3.27 – 3.20 (m, 2H), 2.79 – 2.72 (m, 1H), 2.68 (d, J = 11.6 Hz, 1H), 2.60 (s, 3H), 2.27 (s, 3H), 2.24 – 2.19 (m, 1H), 2.10 (dt, J = 2.0, 11.2 Hz, 1H), 1.88 – 1.77 (m, 2H), 1.62 – 1.44 (m, 3H), 1.36 – 1.23 (m, 2H), 1.17 (d, J = 4.4 Hz, 1H), 0.92 (dd, J = 5.6, 15.2 Hz, 6H), 0.85 – 0.73 (m, 1H).

Example 309

2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-(oxacyclohexan-4-yl)ethan-1-ol **309**



Step 1

2-[(tert-butyldimethylsilicyl)oxy]ethyl acetate **309b**

2-Hydroxylethyl acetate (10 g, 96.06 mmol) and imidazole (6.54 g, 96.06 mmol) were dissolved in dichloromethane (50 mL), and cooled to 0°C, followed by the slow addition of TBSCl (7.91 g, 96.06 mmol). The reaction mixture was stirred at room temperature for 2.0 hours. Dichloromethane (50 mL) was added to the reaction mixture, which was then washed with water (100 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **309b** (13.5 g, 61.82 mmol, yield: 64.36%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.21 (s, 2H), 3.68 (s, 3H), 3.45 (s, 3H), 3.18 (s, 3H).

Step 2

2-[(tert-butyldimethylsilicyl)oxy]-*N*-methoxy-*N*-methylacetamide **309c**

N-methoxymethylamine (6.25 g, 64.11 mmol, hydrochloride) and Compound **309b** (7 g, 32.06 mmol) were dissolved in THF (150 mL), and cooled to 0°C, followed by the slow dropwise addition of isopropylmagnesium chloride solution (2 M, 32.06 mL). The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was cooled to 0°C, followed by dropwise adding a saturated aqueous ammonium chloride solution (50 mL) and extracting with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **309c** (2.1 g, 9.00 mmol, yield: 28.07%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 2H), 4.11 – 3.99 (m, 2H), 1.21 – 1.12 (m, 3H), 0.84 – 0.80 (m, 9H), 0.03 – 0.03 (m, 6H).

Step 3

2-[(tert-butyldimethylsilyl)oxy]-1-(oxacyclohexan-4-yl)ethan-1-one **309d**

Under the protection of nitrogen, Mg (1.47 g, 60.47 mmol) was suspended in THF (20 mL), followed by the addition of I_2 (195.31 mg, 1.53 mmol) and then the slow dropwise addition of the solution of 4-bromotetrahydropyran (5 g, 30.30 mmol) in tetrahydrofuran (5.0 mL), and the mixture was stirred at room temperature for 1.0 hour. At 0°C, the prepared alkyl magnesium bromide tetrahydrofuran solution was slowly dropwise added to the solution of Compound **309c** (2.1 g, 9.00 mmol) in THF(25 mL). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with methyltert-butyl ether (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **309d** (2.2 g, 8.51 mmol, yield: 28.10%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H), 3.95 – 3.83 (m, 1H), 3.54 – 3.31 (m, 4H), 2.98 – 2.86 (m, 1H), 1.77 – 1.73 (m, 2H), 1.35 – 1.23 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

Step 4

(3*R*)-4-{2-[6-(1-{2-[(tert-butyldimethylsilyl)oxy]-1-(oxacyclohexan-4-yl)ethyl}azacyclobutan-3-yl)-1-fluoro-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluorobenzoyl}-3-methylmorpholine **309e**

Compound **145d** (64 mg, 150.07 μmol) and Compound **309d**(77.57 mg, 300.15 μmol) were dissolved in methanol (10.0 mL). Zinc chloride (40.91 mg, 300.15 μmol) was added, and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (28.29 mg, 450.22 μmol) and stirring at 50°C for 11.0 hours. A saturated aqueous sodium bicarbonate solution (50 mL) was added, and the mixture was then extracted with dichloromethane (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **309e** (40 mg, 59.80 μmol, yield: 39.85%).

MS m/z (ESI): 669.2[M+1]

Step 5

2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-(oxacyclohexan-4-yl)ethan-1-ol **309**

Compound **309e** (40 mg, 59.80 μmol) was dissolved in dichloromethane (1.0 mL), the reaction mixture was cooled to 0°C, followed by the addition of trifluoroacetic acid (3 g, 26.31 mmol, 2.03 mL), and the mixture was stirred at 25°C for 48.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (10 mL) and a 10% aqueous sodium hydroxide solution (20 mL), and the reaction mixture was then stirred for 0.5 hours. The mixture was extracted with dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 20%-50%), to obtain the title Compound **309** (8.57 mg, 15.45 μmol, yield: 25.84 %) as yellow solid.

MS m/z (ESI): 555.3[M+1]

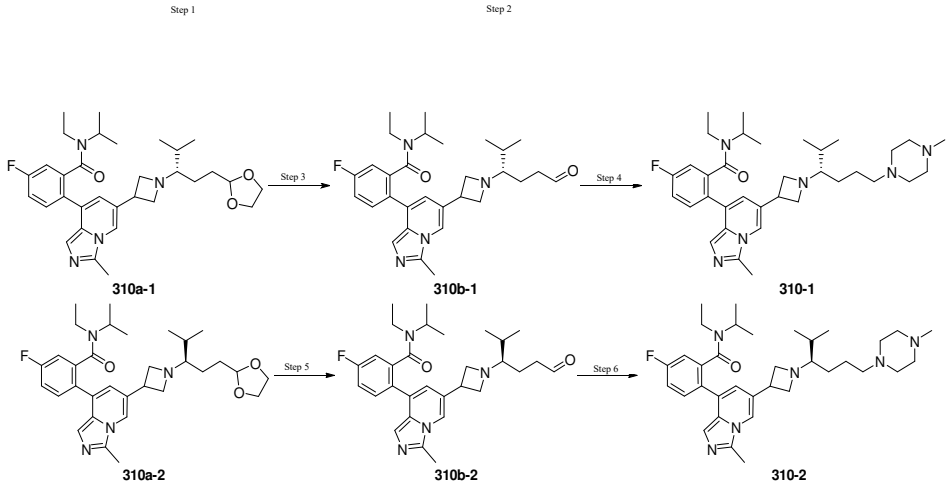
^{1}H NMR (400 MHz, CD_3OD) δ 7.91 – 7.73 (m, 1H), 7.65 – 7.51 (m, 1H), 7.38 – 7.16 (m, 2H), 6.90 – 6.64 (m, 1H),4.64 – 4.04 (m, 2H), 4.01 – 3.92 (m, 2H), 3.84 – 3.52 (m, 7H), 3.49 – 3.34 (m, 5H), 3.17 – 2.71 (m, 2H), 2.60 (s, 3H), 2.39 -2.29 (m, 1H), 1.90 – 1.78 (m, 1H), 1.69 – 1.41 (m, 4H), 1.36 – 1.12 (m, 2H), 0.88 – 0.54 (m, 1H).

Examples 310-1 and 310-2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310-1**

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-

yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310-2**



Step 1

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **310a**

Compound **90b** (400 mg, 1.01 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (261.94 mg, 1.52 mmol) were dissolved in methanol (8.0 mL), followed by the addition of $ZnCl_2$ (276.40 mg, 2.03 mmol), and the mixture was stirred at 55°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (191.16 mg, 3.04 mmol) and stirring at 55°C for 11 hour. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then stirred for 30 min and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **310a** (500 mg, 907.93 μmol, yield: 89.54%)

MS m/z (ESI): 551.3 [M+1]

Step 2

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **310a-1**

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **310a-2**

Compound **310a** (500 mg, 907.93 μmol) was separated and purified by the chiral preparative SFC (preparative column: Daicel Chiralcel OD (250*30 mm, 10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 35%), to obtain the title Compounds **310a-1** (165 mg, 299.62 μmol, yield: 33%) and **310a-2** (155 mg, 281.46 μmol, yield: 31%).

Single-configuration Compound 310a-1:

MS m/z (ESI):551.2 [M+1]

Chiral HPLC analysis: retention time: 1.456 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 310a-2:

MS m/z (ESI):551.2 [M+1]

Chiral HPLC analysis: retention time: 1.710 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310b-1**

Compound **310a-1** (165 mg, 299.62 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 0.3 mL). The mixture was stirred at 55°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (10 mL) and water (5 mL) and regulating to pH ≥ 7 with a 10 % aqueous NaOH solution, and the reaction mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and

concentrated under a reduced pressure, to obtain the crude product of title Compound **310b-1** (150 mg, 296.06 μmol,yield: 98.81%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 310b-1:

MS m/z (ESI): 507.2 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310-1**

The crude product of Compound **310b-1** (75.00 mg, 148.03 μmol) and 1-methylpiperazine (17.79 mg, 177.64 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (8.89 mg, 148.03 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (27.91 mg, 444.09 μmol) was added, allowing for reacting at 25°C for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%). The title Compound **310-1** (12 mg, 20.31 μmol, yield: 13.72%) was obtained.

Single-configuration Compound 310-1:

MS m/z (ESI):591.6 [M+1]

Chiral SFC: retention time: 1.117 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.72 – 7.62 (m, 1H), 7.42 – 7.24 (m, 2H), 7.07 – 7.00 (m, 1H), 6.75 (d, J = 17.6 Hz, 1H), 3.59 – 3.41 (m, 4H), 3.30 – 3.25 (m, 1H), 3.17 – 3.02 (m, 2H), 2.99 – 2.86 (m, 1H), 2.58 (s, 3H), 2.41 – 2.17 (m, 9H), 2.14 – 2.08 (m, 3H), 2.02 (s, 1H), 1.77 – 1.64 (m, 1H), 1.50 – 1.35 (m, 2H), 1.31 – 1.03 (m, 3H), 0.96 – 0.68 (m, 13H), 0.28 (d, J = 6.4 Hz, 2H).

Step 5

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310b-2**

Compound **310a-2** (155.00 mg, 281.46 μmol) was dissolved in acetonitrile (3.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 2 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL) and regulating to pH ≥ 7 with a 10 % aqueous NaOH solution, and the reaction mixture was extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **310b-2** (142 mg, 280.27 μmol, yield: 99.58%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 310b-2:

MS m/z (ESI): 507.3 [M+1]

Step 6

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **310-2**

The crude product of Compound **310b-2** (71.00 mg, 140.14 μmol) and 1-methylpiperazine (16.84 mg, 168.16 μmol) were dissolved in methanol (5.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (26.42 mg, 420.41 μmol) was added, allowing for reacting at 25°C for 11.0 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%). The title Compound **310-2** (6.86 mg, 11.61 μmol, yield: 8.29%) was obtained.

Single-configuration Compound 310-2:

MS m/z (ESI):591.7 [M+1]

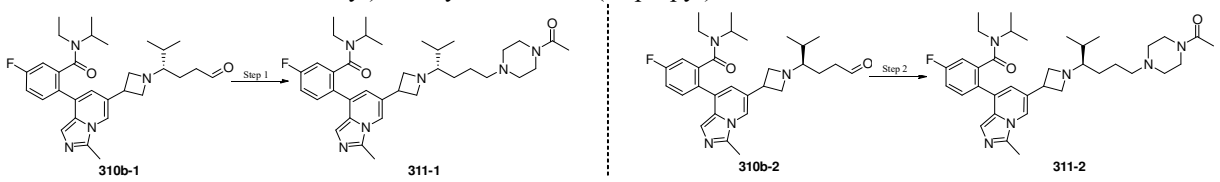
Chiral SFC: retention time: 0.827 min; chromatographic column: Chiralcel AS-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.88 (m, 1H), 7.75 – 7.67 (m, 1H), 7.43 – 7.10 (m, 3H), 6.97 – 6.83 (m, 1H),4.81 – 4.24 (m, 2H), 3.87 – 3.33 (m, 5H), 3.30 – 2.69 (m, 4H), 2.66 (s, 3H), 2.61 – 2.17 (m, 11H), 1.93 – 1.81 (m, 1H), 1.68 -1.51 (m, 2H), 1.47 – 0.74 (m, 15H), 0.30 (br d, J = 6.8 Hz, 2H).

Examples 311-1 and 311-2

2-(6-{1-[(3*S*)-6-(4-acetylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **311-1**

2-(6-{1-[(3*R*)-6-(4-acetylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **311-2**



Step 1

2-(6-{1-[(3*S*)-6-(4-acetylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **311-1**

The crude product of Compound **310b-1** (75.00 mg, 148.03 μmol) and 1-(piperazin-1-yl)ethan-1-one (22.77 mg, 177.64 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (8.89 mg, 148.03 μmol), and the mixture was stirred at room temperature for 1.0 hour.Sodium cyanoborohydride (27.91 mg, 444.09 μmol) was added, allowing for reacting at 25℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%). The title Compound **311-1** (13 mg, 21.01 μmol, yield: 14.19%) was obtained as yellow solid.

Single-configuration Compound 311-1:

MS m/z (ESI):619.5 [M+1]

Chiral SFC: retention time: 1.268 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.72 – 7.64 (m, 1H), 7.43 – 7.27 (m, 2H), 7.07 – 6.99 (m, 1H), 6.84 – 6.72 (m, 1H), 3.58 – 3.37 (m, 7H), 3.30 – 3.27 (m, 1H), 3.19 – 3.01 (m, 2H), 2.99 – 2.86 (m, 1H), 2.58 (s, 3H), 2.37 – 2.21 (m, 6H), 2.04 (s, 1H), 1.96 (s, 3H), 1.78 – 1.65 (m, 1H), 1.54 – 1.38 (m, 2H), 1.31 – 1.01 (m, 3H), 0.98 – 0.68 (m, 13H), 0.27 (d, J = 6.4 Hz, 2H).

Step 2

2-(6-{1-[(3*R*)-6-(4-acetylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **311-2**

The crude product of Compound **310b-2** (71.00 mg, 140.14 μmol) and 1-(piperazin-1-yl)ethan-1-one (21.55 mg, 168.16 μmol) were dissolved in methanol (5.0 mL), and stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (26.42 mg, 420.41 μmol) was added, allowing for reacting at 25℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%). The title Compound **311-2** (7.75 mg, 12.52 μmol, yield: 8.94%) was obtained.

Single-configuration Compound 311-2:

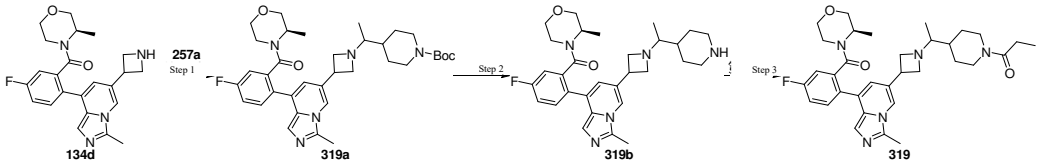
MS m/z (ESI):619.6 [M+1]

Chiral SFC: retention time: 1.089 min; chromatographic column: Chiralcel AS-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.94 – 7.89 (m, 1H), 7.76 – 7.67 (m, 1H), 7.39 – 7.11 (m, 3H), 6.97 – 6.85 (m, 1H),4.78 – 4.26 (m, 2H), 3.86 – 3.37 (m, 9H), 3.29 – 2.97 (m, 2H), 2.66 (s, 3H), 2.52 – 2.37 (m, 5H), 2.28 (br s, 1H), 2.08 (d, J =3.6 Hz, 3H), 1.95 – 1.82 (m, 1H), 1.69 – 1.52 (m, 2H), 1.50 – 1.10 (m, 3H), 0.98 – 0.76 (m, 12H), 0.30 (br d, J = 6.8 Hz, 2H).

Example 319

1-(4-{1-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-yl)propan-1-one **319**



Step 1

4-{1-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-tert-butyl carboxylate **319a**

Compound **134d** (700 mg, 1.71 mmol) and Compound **257a** (467.43 mg, 2.06 mmol) were dissolved in methanol (5.0 mL), followed by the addition of zinc chloride (700.72 mg, 5.14 mmol), and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (323.08 mg, 5.14 mmol) was added, and the mixture was stirred at 50℃ for 12 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **319a** (618 mg, 997.15 μmol, yield: 58.19%) as yellow solid.

MS m/z (ESI):620.4[M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[1-(piperidin-4-yl)ethyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **319b**

Compound **319a** (150 mg, 242.03 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **319b** (120 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 520.2 [M+1]

Step 3

1-(4-{1-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl}piperidin-1-yl)propan-1-one **319**

Triethylamine (57.49 mg, 568.11 μmol) and propionic acid (16.83 mg, 227.25 μmol) were dissolved in dichloromethane (2.0 mL), and cooled to 5°C, followed by the addition of HATU (86.41 mg, 227.25 μmol), and the mixture was stirred for 10 min. The crude product of Compound **319b** (120 mg) was added, and the reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%), to obtain the title Compound **319** (59.89 mg, 104.03 μmol, yield: 43 %) as yellow solid.

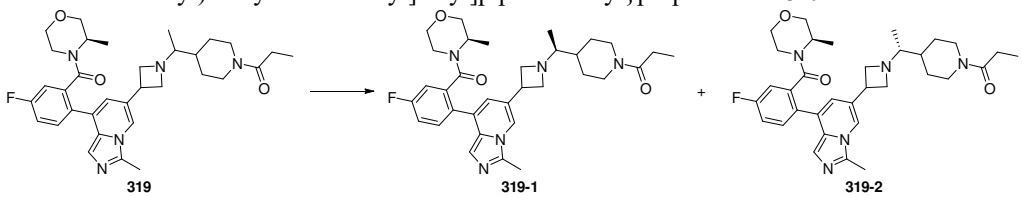
MS m/z (ESI): 576.3 [M+1]

^{1}H NMR (400 MHz,CD_3OD) δ 8.00 – 7.89 (m, 1H), 7.84 – 7.63 (m, 1H), 7.42 – 7.06 (m, 3H), 7.05 – 6.77 (m, 1H), 4.67 – 4.30 (m, 2H), 4.08 – 3.64 (m, 5H), 3.60 – 3.49 (m, 1H), 3.27 – 2.92 (m, 5H), 2.83 – 2.49 (m, 5H), 2.45 – 2.35 (m, 3H), 1.95 – 1.52 (m, 4H), 1.36 – 1.17 (m, 3H), 1.15 – 1.06 (m, 4H), 0.92 – 0.83 (m, 3H), 0.75 – 0.40 (m, 1H).

Examples 319-1 and 319-2

1-{4-[(1*S*)-1-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}propan-1-one **319-1**

1-{4-[(1*R*)-1-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]ethyl]piperidin-1-yl}propan-1-one **319-2**



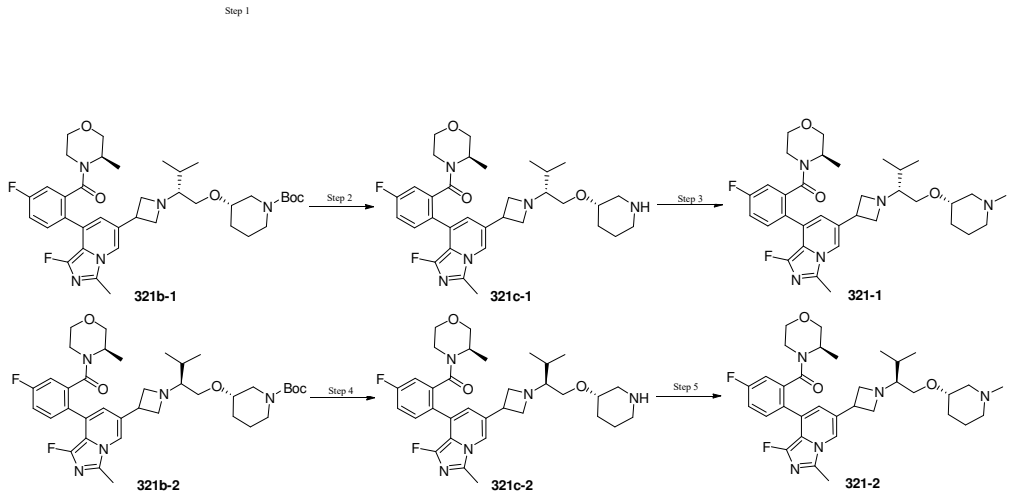
Compound **319** (167.49 mg, 290.93 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), mobile phase: CO_2-EtOH (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **319-1** (38.96 mg, 67.67 μmol, yield: 23.26%) and **319-2** (40.33 mg, 70.05 μmol, yield: 24.08%).

Single-configuration Compound 319-1:
MS m/z (ESI):576.3[M+1]
Chiral HPLC analysis: retention time: 1.415 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.90 (m, 1H), 7.80 – 7.59 (m, 1H), 7.48 – 7.28 (m, 2H), 7.13 – 6.58 (m, 2H), 4.53 – 3.45 (m, 8H), 3.21 – 2.71 (m, 6H), 2.64 – 2.55 (m, 3H), 2.44 – 2.25 (m, 3H), 2.24 – 2.06 (m, 1H), 1.93 – 1.37 (m, 4H), 1.26 – 0.91 (m, 7H), 0.78 – 0.34 (m, 4H).
Single-configuration Compound 319-2:
MS m/z (ESI):576.3[M+1]
Chiral HPLC analysis: retention time: 1.708 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.89 (m, 1H), 7.81 – 7.59 (m, 1H), 7.49 – 7.25 (m, 2H), 7.14 – 6.68 (m, 2H), 4.54 – 4.35 (m, 2H), 3.94 – 3.85 (m, 2H), 3.54 – 3.48 (m, 4H), 3.14 – 2.74 (m, 6H), 2.65 – 2.56 (m, 3H), 2.44 – 2.24 (m, 3H), 2.24 – 2.05 (m, 1H), 1.86 – 1.40 (m, 4H), 1.25 – 0.92 (m, 7H), 0.83 – 0.32 (m, 4H).

Examples 321-1 and 321-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-{[(3*S*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*S*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321-2**



Step 1

(3*S*)-3-[(2*R*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]piperidin-1-tert-butyl carboxylate **321b-1**

(3*S*)-3-[(2*S*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]piperidin-1-tert-butyl carboxylate **321b-2**

Compound **145d** (160 mg, 375.18 μmol) and (3*S*)-3-(3-methyl-2-oxobutoxy)piperidin-1-tert-butyl carboxylate **321a** (117.78 mg, 412.70 μmol, prepared according to the synthesis route of Compound **297e** by using (3*S*)-3-hydroxylpiperidin-1-tert-butyl carboxylate to replace (3*R*)-3-hydroxylpiperidin-1-tert-butyl carboxylate in the first step) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$ (102.27 mg, 750.37 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (70.73 mg, 1.13 mmol), allowing for reacting at 50°C for 11 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the resulting solid was separated and purified by the chiral preparative SFC (preparative column: Phenomenex-Cellulose-2 (250 mm * 30 mm,10 um), mobile phase: CO_2-MeOH (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **321b-1** (55 mg, 79.04 μmol, yield: 21.07%) and **321b-2** (45 mg, 64.67 μmol, yield: 17.24%).
Single-configuration Compound 321b-1:
MS m/z (ESI):696.3 [M+1]

Chiral HPLC analysis: retention time: 1.833 min; chromatographic column: Cellulose-2 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% DEA): elution gradient: 5%-40%.

Single-configuration Compound 321b-2:

MS m/z (ESI):696.2 [M+1]

Chiral HPLC analysis: retention time: 2.004 min; chromatographic column: Cellulose-2 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% DEA): elution gradient: 5%-40%.

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-[(3*S*)-piperidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321c-1**

Compound **321b-1** (55 mg, 79.04 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (999.97 mg, 8.77 mmol, 675.66 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **321c-1** (47 mg, 78.90 μmol, yield: 99.82%) as yellow solid.The crude product was directly used in the next step of reaction without treatment.

MS m/z (ESI):596.2 [M+1]

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-{[(3*S*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321-1**

Compound **321c-1** (47.00 mg, 78.90 μmol) was dissolved in methanol (5.0 mL), followed by the addition of formaldehyde (64.02 mg, 788.96 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (14.87 mg, 236.69 μmol) was added, allowing for reacting at 25°C for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 46%-76%), to obtain the title Compound **321-1** (14.91 mg, 24.45 μmol, yield: 30.99%).

Single-configuration Compound 321-1:

MS m/z (ESI):610.5 [M+1]

Chiral SFC analysis: retention time: 1.152 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH(0.05%DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.35 (m, 2H), 7.24 – 6.99 (m, 2H), 6.79 – 6.51 (m, 1H), 4.65 – 4.11 (m, 1H), 3.80 – 3.68 (m, 2H), 3.64 – 3.50 (m, 3H), 3.41 – 2.71 (m, 9H), 2.61 (s, 3H), 2.60 – 2.29 (m, 2H), 2.27 (s, 3H), 2.17 – 1.71 (m, 6H), 1.58 – 1.08 (m, 4H), 0.96 (br d, J = 6.8 Hz, 3H), 0.90 – 0.53 (m, 4H).

Step 4

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-[(3*S*)-piperidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321c-2**

Compound **321b-2** (45.00 mg, 64.67 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (978.26 mg, 8.58 mmol, 660.99 μL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **321c-2** (38 mg, 63.79 μmol, yield: 98.64%) as yellow oil. The crude product was directly used in the next step of reaction without treatment.

MS m/z (ESI):596.3 [M+1]

Step 5

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*S*)-1-methylpiperidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **321-2**

Compound **321c-2** (39.00 mg, 65.47 μmol) was dissolved in methanol (5.0 mL), followed by the addition of formaldehyde (53.13 mg, 654.67 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (12.34 mg, 196.40 μmol) was added, allowing for reacting at 25°C for 11.0 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and

concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 46%-76%), to obtain the title Compound **321-2** (8.21 mg, 13.46 μmol, yield: 20.57%).

Single-configuration Compound 321-2:

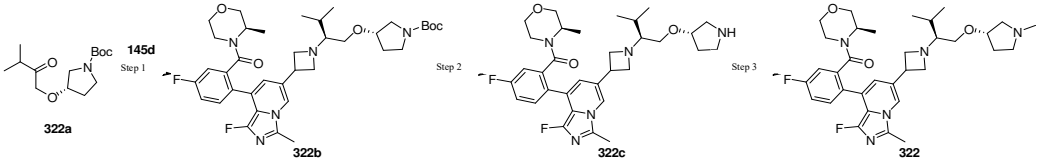
MS m/z (ESI):610.4 [M+1]

Chiral SFC: retention time: 1.139 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz,$CDCl_3$) δ 7.55 – 7.34 (m, 2H), 7.25 – 6.99 (m, 2H), 6.80 – 6.51 (m, 1H), 4.64 – 4.09 (m, 1H), 3.78 – 3.69 (m, 2H), 3.64 – 3.50 (m, 3H), 3.45 – 2.70 (m, 9H), 2.66 – 2.30 (m, 5H), 2.27 (s, 3H), 2.16 – 1.70 (m, 6H), 1.58 -1.10 (m, 4H), 0.96 (br d, J = 6.8 Hz, 3H), 0.90 – 0.57 (m, 4H).

Example 322

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*S*)-1-methylpyrrolidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **322**



Step 1

(3*S*)-3-[(2*S*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutoxy]pyrrolidin-1-tert-butyl carboxylate **322b**

Compound **145d** (80 mg, 187.59 μmol) and (3*S*)-3-(3-methyl-2-oxobutoxy)pyrrolidin-1-tert-butyl carboxylate **322a** (76.35 mg, 281.39 μmol, prepared according to the synthesis route of Compound **297e** by using (3*S*)-3-hydroxylpyrrolidin-1-tert-butyl carboxylate to replace (3*R*)-3-hydroxylpiperidin-1-tert-butyl carboxylate in the first step) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$(51.14 mg, 375.18 μmol), and the mixture was stirred at 55°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (35.37 mg, 562.78 μmol), allowing for reacting at 55°C for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **322b** (60 mg, 88.00 μmol, yield: 46.91%) as yellow oil.

MS m/z (ESI):682.2 [M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-[(3*S*)-pyrrolidin-3-yloxy]butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **322c**

Compound **322b** (60 mg, 88.00 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product of title Compound **322c** (51 mg) was obtained. The crude product was directly used in the next step of reaction without treatment.

MS m/z (ESI):582.3 [M+1]

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-{[(3*S*)-1-methylpyrrolidin-3-yl]oxy}butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8yl)benzoyl]-3-methylmorpholine **322**

The crude product of Compound **322c** (51 mg) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (13.31 mg, 131.51 μmol) and formaldehyde (36.56 mg, 438.37 μmol, 37%purity), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (16.53 mg, 263.02 μmol) was added, allowing for reacting at 25°C for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 40%-70%), to obtain the title Compound **322** (7 mg, 11.75 μmol, yield: 13.40%).

MS m/z (ESI):596.3 [M+1]

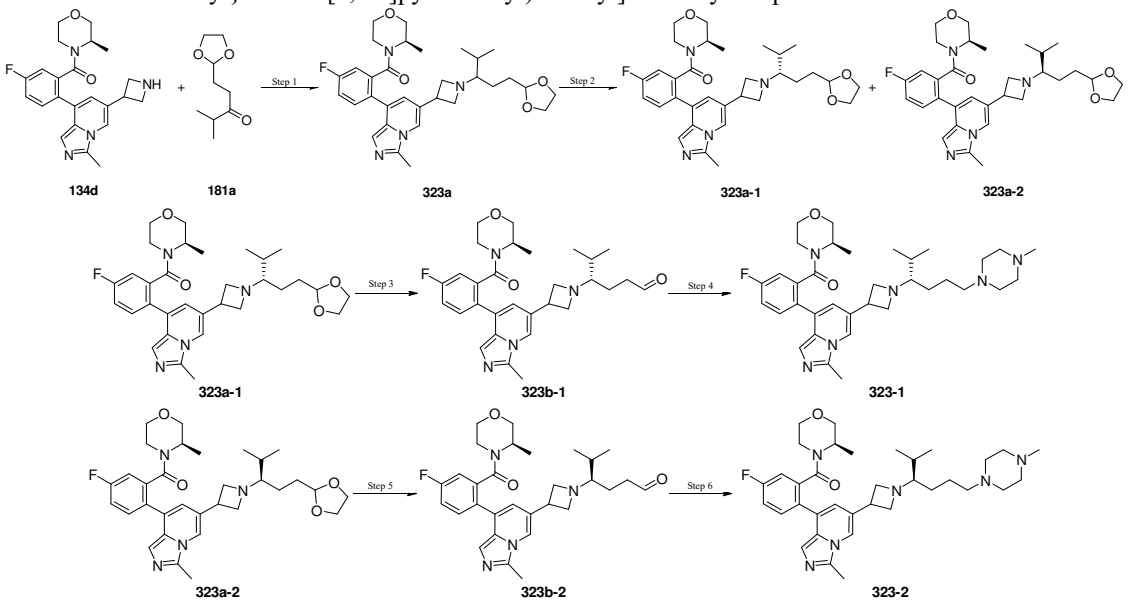
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.79 (m, 1H), 7.63 – 7.23 (m, 3H), 6.81 – 6.49 (m, 1H), 4.46 – 3.41 (m,

8H), 3.24 – 2.66 (m, 6H), 2.63 – 2.57 (m, 1H), 2.55 (s, 3H), 2.48 – 2.21 (m, 5H), 2.17 (s, 3H), 2.03 – 1.88 (m, 1H), 1.78 – 1.54 (m, 2H), 1.26 – 1.04 (m, 2H), 0.89 (d, J = 6.8 Hz, 3H), 0.85 – 0.70 (m, 4H).

Examples 323-1 and 323-2

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **323-1**

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **323-2**



Step 1

(3*R*)-4-[2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **323a**

Compound **134d** (1.37 g, 3.35 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (866.44 mg, 5.03 mmol) were dissolved in methanol (15 mL), followed by the addition of $ZnCl_2$ (914.27 mg, 6.71 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (632.32 mg, 10.06 mmol) and stirring at 50°C for 10 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **323a** (1.5 g, 2.66 mmol, yield: 79.2%).

MS m/z (ESI): 565.3[M+1]

Step 2

(3*R*)-4-[2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **323a-1**

(3*R*)-4-[2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluorobenzoyl]-3-methylmorpholine **323a-2**

Compound **323a** (1.5 g, 2.66 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-[acetonitrile/ethanol (0.1% ammonia water)]; elution gradient: 20%), to obtain the title Compounds **323a-1** (700 mg, 1.24 mmol, yield: 46.67%) and **323a-2** (700 mg, 1.24 mmol, yield: 46.67%).

Single-configuration Compound 323a-1:

MS m/z (ESI):565.3 [M+1]

Chiral HPLC analysis: retention time: 1.292 min; chromatographic column: Chiralcel OD-3 50 x 4.6mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 323a-2:

MS m/z (ESI):565.3 [M+1]

Chiral HPLC analysis: retention time: 1.542 min; chromatographic column: Chiralcel OD-3 50 x 4.6mm I.D., 3 um; mobile phase: CO_2-EtOH (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

(4*S*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexanal **323b-1**

Compound **323a-1** (420.00 mg, 743.77 μmol) was dissolved in acetonitrile (4.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 4.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 11 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **323b-1** (380 mg, 729.88 μmol, yield: 98.13%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 323b-1:

MS m/z (ESI): 521.3 [M+1]

Step 4

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **323-1**

Compound **323b-1**(190.00 mg, 364.94 μmol) and 1-methylpiperazine (73.11 mg, 729.88 μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (21.92 mg, 364.94 μmol), and the mixture was stirred at 25°C for 0.5 hours. Sodium cyanoborohydride (68.80 mg, 1.09 mmol) was added, allowing for reacting 25℃ for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title Compound **323-1** (54.88 mg, 90.74 μmol, yield: 24.86%).

Single-configuration Compound 323-1:

MS m/z (ESI):605.4 [M+1]

Chiral SFC: retention time: 1.174 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.87 (m, 1H), 7.81 – 7.59 (m, 1H), 7.49 – 7.22 (m, 2H), 7.19 – 6.92 (m, 1H), 6.91 – 6.66 (m, 1H), 4.39 – 3.84 (m, 1H), 3.80 – 3.40 (m, 5H), 3.28 – 2.67 (m, 6H), 2.64 – 2.56 (m, 3H), 2.41 – 2.14 (m, 9H), 2.13 – 2.07 (m, 3H), 2.06 – 1.99 (m, 1H), 1.96 – 1.59 (m, 2H), 1.51 – 1.37 (m, 2H), 1.30 – 1.00 (m, 4H), 0.88 – 0.77 (m, 6H), 0.70 – 0.35 (m, 1H).

Step 5

(4*R*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexanal **323b-2**

Compound **323a-2** (400.00 mg, 708.35 μmol) was dissolved in acetonitrile (4.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 4.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 11 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **323b-2** (360 mg, 691.46 μmol, yield: 97.62%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 323b-2:

MS m/z (ESI): 521.3 [M+1]

Step 6

(3*R*)-4-[5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **323-1**

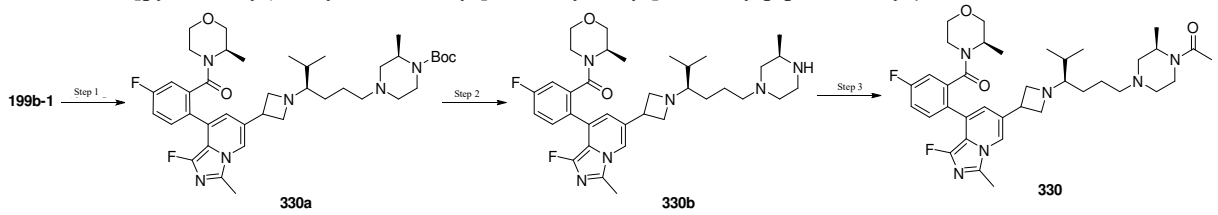
The crude product of Compound **323b-2** (180.00 mg, 345.73 μmol) and 1-methylpiperazine (69.26 mg, 691.46 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (20.76 mg, 345.73 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (65.18 mg, 1.04 mmol) was added, allowing for reacting 25℃ for 9.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title Compound **323-2** (75 mg, 124.01 μmol, yield: 35.87%) as yellow solid.

Single-configuration Compound 323-2:

MS m/z (ESI):605.6 [M+1]
Chiral SFC: retention time: 1.178 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 7.83 (m, 1H), 7.82 – 7.58 (m, 1H), 7.54 – 7.20 (m, 2H), 7.18 – 6.57 (m, 2H), 4.39 – 3.38 (m, 6H), 3.29 – 2.54 (m, 9H), 2.40 – 2.01 (m, 13H), 1.90 – 0.99 (m, 8H), 0.93 – 0.77 (m, 6H), 0.70 – 0.38 (m, 1H).

Example 330

1-{(2*R*)-4-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-methylpiperazin-1-yl}ethan-1-one **330**



Step 1

(2*R*)-4-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*) -3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-methylpiperazin-1-tert-butyl carboxylate **330a**

Compound **199b-1** (150 mg, 278.49 μmol) and (2*R*)-2-methylpiperazin-1-tert-butyl carboxylate (66.93 mg, 334.18 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (1.67 mg, 27.85 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (52.50 mg, 835.46 μmol) was added, allowing for reacting at room temperature for 11 hours under the protection of nitrogen. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title product **330a** (156 mg, 215.80 μmol, yield: 77.49%) as yellow oil.
MS m/z (ESI):723.4 [M+1]

Step 2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-2-methyl-6-[(3*R*)-3-methylpiperazin-1-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **330b**

Compound **330a** (156 mg, 215.80 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 3.0 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined and washed once with saturated brine (50 mL), the organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **330b** (134 mg, 215.16 μmol, yield: 99.71%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 623.3 [M+1]

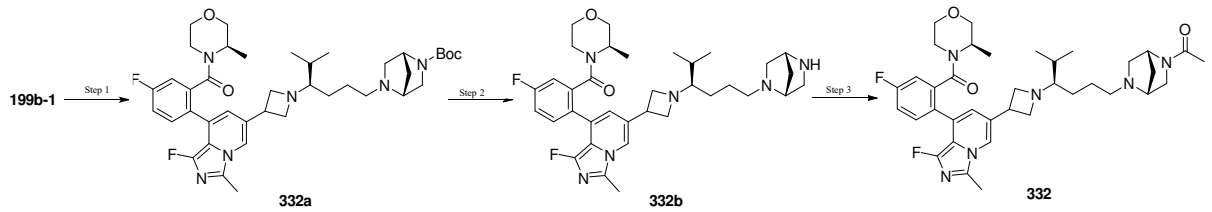
Step 3

1-{(2*R*)-4-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-methylpiperazin-1-yl}ethan-1-one **330**

Triethylamine (65.32 mg, 645.48 μmol) and Compound **330b** (134 mg, 215.16 μmol) were dissolved in dichloromethane (5.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (26.36 mg, 258.19 μmol). The reaction mixture was stirred at room temperature for 12 hours. Water (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:34%-64%). The title Compound **330** (64.96 mg, 97.71 μmol, yield: 45.41%) was obtained as yellow solid.
MS m/z (ESI): 665.4 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.35 (m, 2H), 7.25 – 7.06 (m, 2H), 6.83 – 6.56 (m, 1H), 4.79 – 4.10 (m, 2H), 3.99 – 3.22 (m, 8H), 3.13 (br s, 2H), 3.02 – 2.65 (m, 4H), 2.61 (s, 3H), 2.38 – 2.17 (m, 2H), 2.11 – 2.04 (m, 4H), 2.03 – 1.77 (m, 3H), 1.71 (br s, 2H), 1.56 – 1.38 (m, 3H), 1.34 – 1.22 (m, 4H), 1.20 – 1.06 (m, 1H), 0.97 – 0.87 (m, 6H), 0.84 – 0.57 (m, 1H).

Example 332

1-[(1*R*,4*R*)-5-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethan-1-one **332**



Step 1

(1*R*,4*R*)-5-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,5-diazadicyclo[2.2.1]heptan-2-tert-butyl carboxylate **332a**

Compound **199b-1** (180 mg, 334.18 μmol) and (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-tert-butyl carboxylate (79.51 mg, 401.02 μmol) were dissolved in methanol (4.0 mL), followed by the addition of acetic acid (20.07 mg, 334.18 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (63.00 mg, 1.00 mmol) was added, allowing for reacting at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **332a** (150 mg, 208.08 μmol, yield: 62.26%) as yellow solid.

MS m/z (ESI):721.5 [M+1]

Step 2

(1*R*,4*R*)-2-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,5-diazabicyclo[2.2.1]heptane **332b**

Compound **332a** (150 mg, 208.08 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (20 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **332b** (120 mg, 193.31 μmol, yield: 92.90%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 621.4 [M+1]

Step 3

1-[(1*R*,4*R*)-5-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethan-1-one **332**

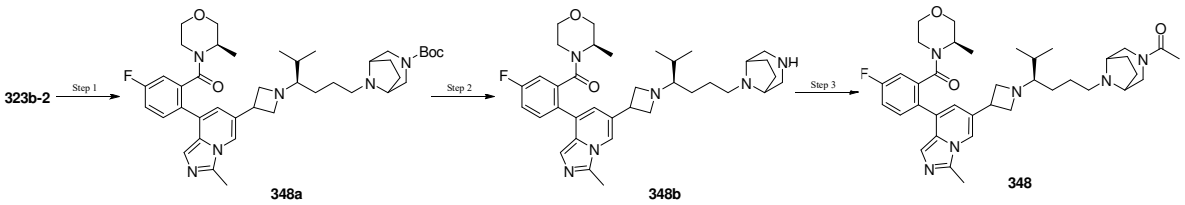
Triethylamine (58.68 mg, 579.92 μmol) and Compound **332b** (120 mg, 193.31 μmol) were dissolved in dichloromethane (2.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (39.47 mg, 386.61 μmol). The reaction mixture was stirred at room temperature for 1.0 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:27%-57%). The title Compound **332** (27.93 mg, 42.14 μmol, yield: 21.80%) was obtained as yellow solid.

MS m/z (ESI): 663.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.74 (m, 1H), 7.70 – 7.11 (m, 3H), 6.90 – 6.34 (m, 1H), 4.45 – 3.88 (m, 2H), 3.77 – 3.38 (m, 7H), 3.25 – 2.65 (m, 8H), 2.59 – 2.52 (m, 3H), 2.45 – 2.31 (m, 3H), 2.05 – 1.80 (m, 4H), 1.76 – 1.49 (m, 3H), 1.44 – 1.05 (m, 6H), 0.90 – 0.52 (m, 7H).

Example 348

1-{8-[(4*R*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-3,8-diazabicyclo[3.2.1]oct-3-yl}ethan-1-one **348**



Step 1

8-[(4*R*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-3,8-diazabicyclo[3.2.1]octan-3-tert-butyl carboxylate **348a**

Compound **323b-2** (130 mg, 249.69 μmol) and 3,8-diazabicyclo[3.2.1]octan-3-tert-butyl carboxylate (106.01 mg, 499.39 μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (14.99 mg, 249.69 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (47.07 mg, 749.08 μmol) was added, allowing for reacting at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **348a** (150 mg, 209.23 μmol, yield: 83.79%) as yellow solid.

MS m/z (ESI):717.2 [M+1]

Step 2

8-[(4*R*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-3,8-diazabicyclo[3.2.1]octane **348b**

Compound **348a** (150 mg, 209.23 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (15 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **348b** (120 mg, 194.55 μmol, yield: 92.98%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 523.1 [M+1]

Step 3

1-{8-[(4*R*)-4-[3-(8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-3,8-diazabicyclo[3.2.1]oct-3-yl}ethan-1-one **348**

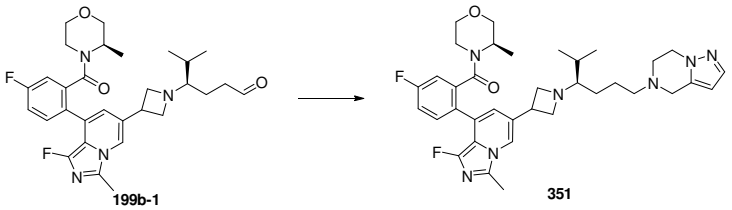
Triethylamine (59.06 mg, 583.65 μmol) and Compound **348b** (120 mg, 194.55 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (39.72 mg, 389.10 μmol). The reaction mixture was stirred at room temperature for 1.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:26%-56%). The title Compound **348** (46.78 mg, 71.00 μmol, yield: 36.50%) was obtained as yellow solid.

MS m/z (ESI): 659.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 – 7.83 (m, 1H), 7.81 – 7.60 (m, 1H), 7.49 – 7.26 (m, 2H), 7.12 – 6.93 (m, 1H), 6.91 – 6.60 (m, 1H), 4.37 – 3.83 (m, 2H), 3.73 – 3.35 (m, 6H), 3.24 – 2.62 (m, 10H), 2.62 – 2.58 (m, 3H), 2.29 – 2.18 (m, 2H), 2.10 – 2.01 (m, 1H), 1.96 – 1.88 (m, 3H), 1.82 – 1.65 (m, 3H), 1.52 – 1.38 (m, 3H), 1.35 – 1.20 (m, 3H), 1.19 – 1.12 (m, 1H), 1.08 – 0.98 (m, 1H), 0.90 – 0.79 (m, 6H), 0.70 – 0.37 (m, 1H).

Example 351

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(3*R*)-2-methyl-6-{4*H*,5*H*,6*H*,7*H*-pyrazolo[1,5-a]pyrazin-5-yl}hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **351**



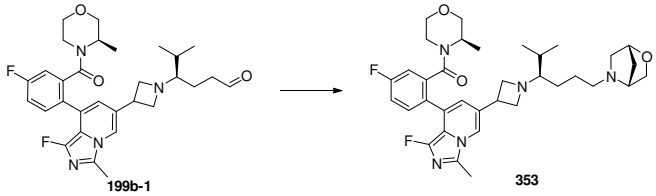
Compound **199b-1** (100 mg, 185.66 μmol) and 4*H*,5*H*,6*H*,7*H*-pyrazolo[1,5-a]pyrazine (59.27 mg, 371.31 μmol, hydrochloride) were dissolved in methanol (2.0 mL), followed by the addition of triethylamine (70 mg, 691.77 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (35.00 mg, 556.97 μmol) was added, allowing for reacting at room temperature for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:36%-66%). The title Compound **351** (21.18 mg, 32.80 μmol, yield: 17.67%) was obtained as yellow solid.

MS m/z (ESI): 646.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.75 (m, 1H), 7.71 – 6.33 (m, 5H), 5.97 (s, 1H), 4.41 – 3.36 (m, 11H), 3.27 – 2.52 (m, 10H), 2.49 – 2.42 (m, 2H), 2.11 – 2.01 (m, 1H), 1.78 – 1.04 (m, 7H), 0.91 – 0.55 (m, 7H).

Example 353

(1*R*,4*R*)-5-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-oxa-5-azabicyclo[2.2.1]heptane **353**



Compound **199b-1** (110 mg, 204.22 μmol) and (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (55.38 mg, 408.45 μmol, hydrochloride) were dissolved in methanol (3.0 mL), followed by the addition of triethylamine (62.00 mg, 612.67 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (38.50 mg, 612.67 μmol) was added, allowing for reacting at room temperature for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:35%-65%). The title Compound **353** (52.61 mg, 84.61 μmol, yield: 41.43%) was obtained as yellow solid.

MS m/z (ESI): 622.4 [M+1]

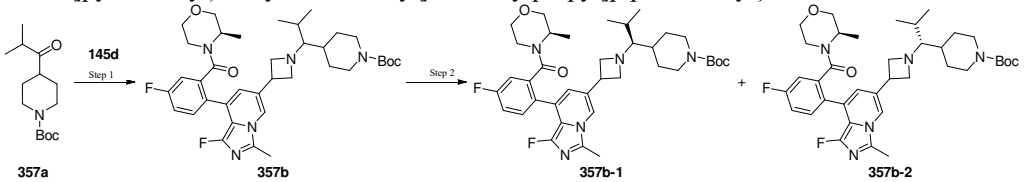
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.77 (m, 1H), 7.64 – 7.21 (m, 3H), 6.84 – 6.43 (m, 1H), 4.44 – 3.33 (m, 11H), 3.27 – 2.60 (m, 6H), 2.55 (s, 3H), 2.48 – 2.29 (m, 3H), 2.06 – 1.99 (m, 1H), 1.75 – 1.63 (m, 2H), 1.55 – 1.47 (m, 1H), 1.45 – 1.04 (m, 6H), 0.88 – 0.57 (m, 7H).

Examples 357-1 and 357-2

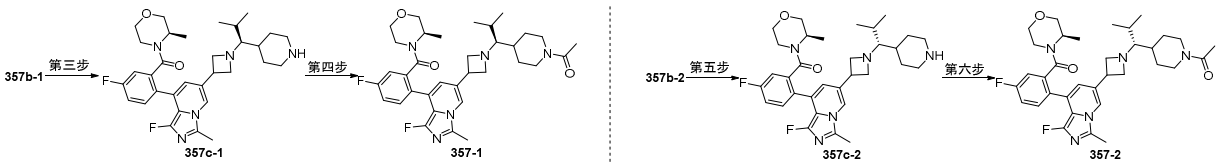
1-{4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-yl}ethan-1-one **357-1**

1-{4-[(1R)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3R)-3-methylmorpholine-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azetidin-1-yl]-2-methylpropyl]piperidin-1-yl}ethan-1-one

1-{4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-yl}ethan-1-one **357-2**



Step 3 Step 4 Step 5 Step 6



Step 1

4-{1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl}piperidin-1-tert-butyl carboxylate **357b**

Compound **145d** (526 mg, 1.23 mmol) and 4-(2-methylpropionyl)piperidin-1-tert-butyl formate **357a** (450 mg, 1.76 mmol) were dissolved in methanol (5.0 mL), followed by the addition of zinc chloride (336.22 mg, 2.47 mmol), and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (232.53 mg, 3.70 mmol) was added, and the mixture was stirred at 50°C for 12 hours. In view of a large amount of leftover raw materials, 4- (2-methylpropionyl)piperidin-1-tert-butyl formate **357a** (450 mg, 1.76 mmol) was supplemented and dissolved in methanol (5.0 mL), zinc chloride (336.22 mg, 2.47 mmol) was added, and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (232.53 mg, 3.70 mmol) was added, and the mixture was stirred at 50°C for 12 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **357b** (500 mg, 750.96 μmol, yield: 60.88%) as yellow oil.

MS m/z (ESI):666.4[M+1]

Step 2

4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-tert-butyl carboxylate **357b-1**

4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-tert-butyl carboxylate **357b-2**

Compound **357b** (500 mg, 750.96 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL DAICEL ChiralPak AD, (250*30 mm, 10 um), mobile phase: carbon dioxide-ethanol (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **357b-1** (200 mg, 300.39 μmol, yield: 40%) and **357b-2** (190 mg, 285.37 μmol, yield: 38.0%).

Single-configuration Compound 357b-1:

MS m/z (ESI):666.4[M+1]

Chiral HPLC analysis: retention time: 1.086 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-EtOH (0.05% isopropylamine): elution gradient: 5%-40%.

Single-configuration Compound 357b-2:

MS m/z (ESI):666.5[M+1]

Chiral HPLC analysis: retention time: 1.446 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-EtOH (0.05% isopropylamine): elution gradient: 5%-40%.

Step 3

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*S*)-2-methyl-1-(piperidin-4-yl)propyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **357c-1**

Compound **357b-1** (200 mg, 300.39 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (3.0 mL), regulated to PH = 10 by adding a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **357c-1** (160 mg, 282.84 μmol, yield: 94.16%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 566.3 [M+1]

Step 4

1-{4-[(1*S*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-yl}ethan-1-one **357-1**

Triethylamine (85.86 mg, 848.51 μmol) and Compound **357c-1** (160 mg, 282.84 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (57.75 mg, 565.68 μmol). The reaction mixture was stirred at room temperature for 1.0 hours. A saturated aqueous sodium bicarbonate solution

(10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 32%-62%), to obtain the title Compound **357-1** (55.00 mg, 90.50 μmol, yield: 32.00%) as yellow solid.

MS m/z (ESI): 608.3 [M+1]

Chiral SFC analysis: retention time: 1.275 min; chromatographic column: Chiralpak OD-3 50 x 4.6mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% isopropylamine): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 – 7.65 (m, 1H), 7.62 – 7.23 (m, 3H), 6.96 – 6.32 (m, 1H), 4.49 – 3.89 (m, 2H), 3.85 – 3.41 (m, 6H), 3.21 – 2.65 (m, 6H), 2.59 – 2.51 (m, 3H), 2.46 – 2.31 (m, 2H), 2.02 – 1.87 (m, 4H), 1.81 – 1.69 (m, 1H), 1.68 – 1.48 (m, 3H), 1.37 – 1.02 (m, 4H), 0.94 – 0.60 (m, 7H).

Step 5

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(1*R*)-2-methyl-1-(piperidin-4-yl)propyl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **357c-2**

Compound **357b-2** (190 mg, 285.37 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (10.0 mL), regulated to PH = 10 by adding a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **357c-2** (160 mg, 282.84 μmol, yield: 99.11%) as yellow oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 566.3 [M+1]

Step 6

1-{4-[(1*R*)-1-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-2-methylpropyl]piperidin-1-yl}ethan-1-one **357-2**

Triethylamine (143.10 mg, 1.41 mmol) and Compound **357c-2**(160 mg, 282.84 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (57.75 mg, 565.68 μmol). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 32%-62%), to obtain the title Compound **357-2** (39.59 mg, 65.14 μmol, yield: 23.03 %) as yellow solid.

MS m/z (ESI): 608.4 [M+1]

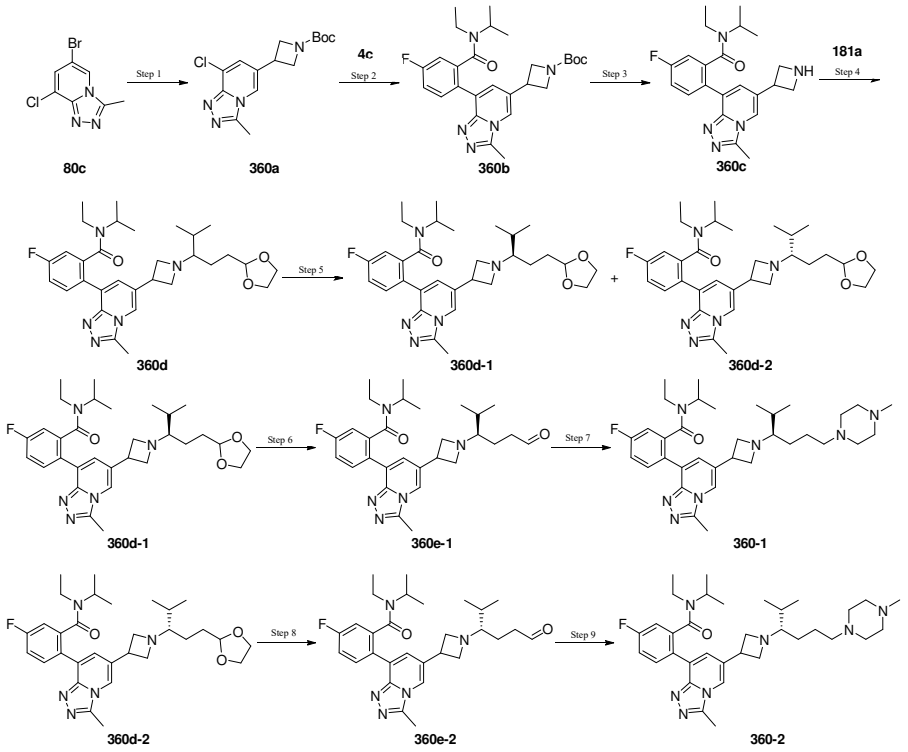
Chiral SFC analysis: retention time: 1.273 min; chromatographic column: Chiralpak OD-3 50 x 4.6mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% isopropylamine): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.75 (m, 1H), 7.61 – 7.25 (m, 3H), 6.85 – 6.52 (m, 1H), 4.47 – 3.46 (m, 8H), 3.11 (s, 3H), 3.01 – 2.77 (m, 3H), 2.55 (s, 3H), 2.45 – 2.31 (m, 2H), 2.01 – 1.89 (m, 4H), 1.82 – 1.71 (m, 1H), 1.68 – 1.50 (m, 3H), 1.42 – 1.06 (m, 4H), 0.92 – 0.71 (m, 7H).

Examples 360-1 and 360-2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360-1**

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360-2**



Step 1

3-{8-chloro-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-yl}azacyclobutan-1-tert-butyl carboxylate **360a**

Under the protection of nitrogen, 1,2-dibromoethane (184.47 mg, 981.97 μmol) was dissolved in DMAc (20 mL), followed by the addition of zinc powder (600.53 mg, 9.18 mmol). The mixture was stirred at 70°C for 10 min, and then cooled to room temperature, followed by the slow dropwise addition of TMSCl (76.75 mg, 706.45 μmol) to the reaction mixture, and after the dropwise addition, the reaction mixture was further stirred at 25° for 30 min. Then, the solution of 3-iodoazacyclobutan-1-tert-butyl carboxylate (2 g, 7.06 mmol) in DMAc (10 mL) was dropwise added to the reaction mixture. The reaction mixture was warmed to 40°C and stirred for 1.0 hours, until the disappearance of noticeable solid precipitates in the mixture. The reaction mixture was cooled to 25°C, followed by the addition of Compound **80c** (1.39 g, 5.62 mmol), $Pd_2(dba)_3$ (406.21 mg, 706.45 μmol) and tri(2-furyl)phosphine (164.02 mg, 706.45 μmol) to the reaction, and the reaction mixture was then subjected to nitrogen substitution three times, warmed to 70°C and stirred to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (150 mL) and extracting with ethyl acetate (100 mL x 3). The organic phase was washed with water (100 mL × 2) and saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **360a** (760 mg, 2.35 mmol, yield: 33.33%) as white solid.

MS m/z (ESI): 323.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.41 (s, 1H), 4.40 (t, J = 8.8 Hz, 2H), 3.96 (dd, J = 5.2, 8.4 Hz, 2H), 3.77 – 3.68 (m, 1H), 2.77 (s, 3H), 1.49 (s, 9H).

Step 2

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **360b**

Compound **360a** (760 mg, 2.35 mmol), Compound **4c** (1.46 g, 2.83 mmol) and potassium phosphate (1.50 g, 7.06 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). $Pd(dtbpf)Cl_2$ (153.45 mg, 235.45 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **360b** (781 mg, 1.58 mmol, yield: 66.93%).

MS m/z (ESI): 496.6 [M+1]

Step 3

2-[6-(azacyclobutan-3-yl)-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide

360c

Compound **360b** (781 mg, 1.58 mmol) were dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by the adding of dichloromethane (30 mL), regulating to PH > 7 with a 10% aqueous sodium hydroxide solution (40 mL) and extracting for separation, and the aqueous phase was extracted with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **360c** (623 mg, 1.58 mmol, yield: 99.96%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 396.1 [M+1]

Step 4

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **360d**

Compound **360c** (623 mg, 1.58 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (408.16 mg, 2.37 mmol) were dissolved in methanol (20 mL), followed by the addition of $ZnCl_2$(430.70 mg, 3.16 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (297.87 mg, 4.74 mmol) and stirring at 50℃ for 11 hour. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the crude product of title Compound **360d** (450 mg).

MS m/z (ESI): 552.2 [M+1]

Step 5

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **360d-1**

2-(6-{1-[(3S)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azetidin-3-yl}-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-N-ethyl-5-fluoro-N-(propan-2-yl)benzamide

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **360d-2**

The crude product of Compound **360d** (450 mg) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 45%), to obtain the crude products of title Compounds **360d-1** (134 mg, 242.89 μmol, yield: 15.37%) and **360d-2** (120 mg, 217.51 μmol, yield: 13.77%)

Single-configuration Compound 360d-1:

MS m/z (ESI):552.3 [M+1]

Chiral HPLC analysis: retention time: 1.975 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 360d-2:

MS m/z (ESI):552.3 [M+1]

Chiral HPLC analysis: retention time: 1.664 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 6

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360e-1**

Compound **360d-1** (134 mg, 242.89 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH > 7 using a 10 % aqueous NaOH solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **360e-1** (123 mg, 242.30 μmol, yield: 99.76%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 360e-1:

MS m/z (ESI): 508.2 [M+1]

Step 7

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360-1**

The crude product of Compound **360e-1** (123 mg, 242.30 μmol) and 1-methylpiperazine (29.12 mg, 290.76 μmol)

were dissolved in methanol (10 mL). Acetic acid (1.46 mg, 24.23 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (45.68 mg, 726.89 μmol) was added, allowing for reacting at room temperature for 11 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%). The title Compound **360-1** (10.2 mg, 17.24 μmol, yield: 7.11%) was obtained as yellow solid.

Single-configuration Compound 360-1:

MS m/z (ESI):592.4 [M+1]

Chiral SFC: retention time: 1.180 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.71 (m, 2H), 7.50 – 7.34 (m, 1H), 7.26 – 7.09 (m, 2H), 4.45 – 3.37 (m, 5H), 3.26 – 2.89 (m, 3H), 2.78 (s, 3H), 2.64 – 2.04 (m, 13H), 1.86 – 1.72 (m, 2H), 1.62 – 1.48 (m, 2H), 1.41 – 1.03 (m, 3H), 1.01 – 0.76 (m, 12H), 0.33 (br d, J = 6.4 Hz, 2H).

Step 8

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360e-2**

Compound **360d-2** (120 mg, 217.51 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH > 7 using a 10 % aqueous NaOH solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **360e-2** (110 mg, 216.69 μmol, yield: 99.62%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 360e-2:

MS m/z (ESI): 508.3[M+1]

Step 9

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **360-2**

The crude product of Compound **360e-2** (110 mg, 216.69 μmol) and 1-methylpiperazine (26.04 mg, 260.03 μmol) were dissolved in methanol (10 mL). Acetic acid (1.30 mg, 21.67 μmol) was added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (40.85 mg, 650.07 μmol) was added, allowing for reacting at room temperature for 11 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%). The title Compound **360-2** (25.85 mg, 43.68 μmol, yield: 20.16%) was obtained as yellow solid.

Single-configuration Compound 360-2:

MS m/z (ESI):592.4 [M+1]

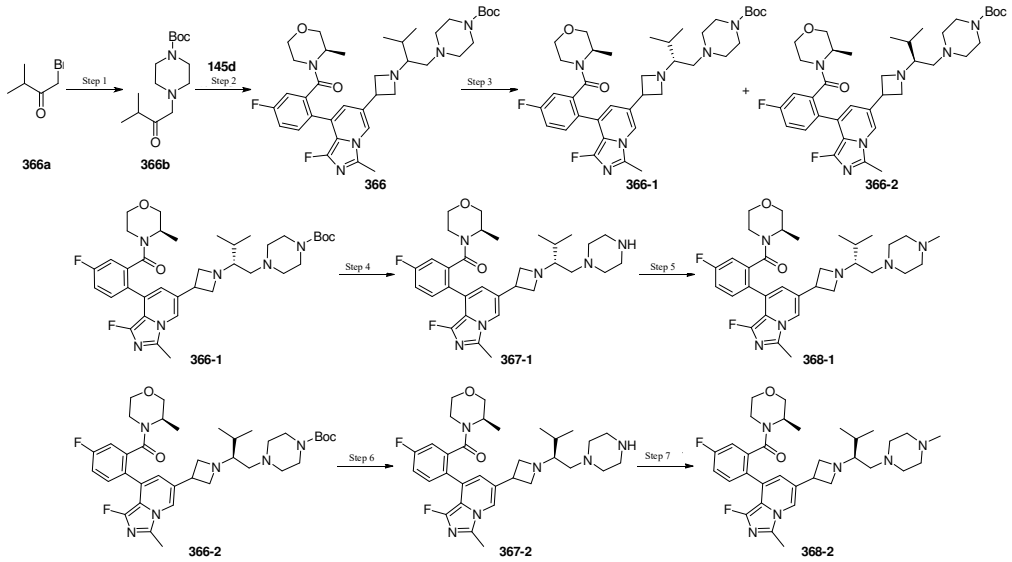
Chiral SFC: retention time: 1.183 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.70 (m, 2H), 7.49 – 7.35 (m, 1H), 7.26 – 7.07 (m, 2H), 4.47 – 3.37 (m, 5H), 3.25 – 2.90 (m, 3H), 2.78 (s, 3H), 2.58 – 2.02 (m, 13H), 1.89 – 1.72 (m, 2H), 1.61 – 1.47 (m, 2H), 1.44 – 1.05 (m, 3H), 0.99 – 0.76 (m, 12H), 0.33 (br d, J = 6.4 Hz, 2H).

Examples 368-1 and 368-2

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **368-1**

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **368-2**



Step 1

4-(3-methyl-2-oxobutyl)piperazin-1-tert-butyl carboxylate **366b**

Piperazin-1-tert-butyl carboxylate (1.0 g, 5.37 mmol) was dissolved in DMF(15 mL), followed by the addition of 1-bromo-3-methyl-but-2-one **366a** (930.36 mg, 5.64 mmol) and potassium carbonate (2.23 g, 16.11 mmol L), and the mixture was stirred at 80°C for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **366b** (1.2 g, 4.44 mmol, yield: 82.67%) as yellow oil.

MS m/z (ESI): 271.3 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 – 3.44 (m, 4H), 3.28 (s, 2H), 2.76 – 2.65 (m, 1H), 2.49 – 2.40 (m, 4H), 1.46 (s, 9H), 1.10 (d, J = 7.0 Hz, 6H).

Step 2

4-{2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl}piperazin-1-tert-butyl carboxylate **366**

Compound **145d** (830 mg, 1.95 mmol) and Compound **366b** (631.45 mg, 2.34 mmol) were dissolved in methanol (12 mL), followed by the addition of $ZnCl_2$ (530.54 mg, 3.89 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (366.92 mg, 5.84 mmol) and stirring at 50°C for 12 hour. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **366** (650 mg, 954.72 μmol, yield: 49.05%).

MS m/z (ESI): 681.5 [M+1]

Step 3

4-[(2*R*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **366-1**

4-[(2*S*)-2-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **366-2**

Compound **366** (600 mg, 881.28 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IK (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-ethanol (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **366-1** (300 mg, 440.64 μmol, yield: 50%) and **366-2** (200 mg, 293.76 μmol, yield: 33.3%)

Single-configuration Compound 366-1:

MS m/z (ESI):681.8 [M+1]

Chiral HPLC analysis: retention time: 1.549 min; chromatographic column: Chiralpak IK-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 366-2:

MS m/z (ESI):681.8 [M+1]

Chiral HPLC analysis: retention time: 1.673 min; chromatographic column: Chiralpak IK-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 4

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **367-1**

Compound **366-1** (150.00 mg, 220.32 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **367-1** (130 mg), of which 100 mg of the crude product was directly used in the next step of reaction without purification. 30 mg of the crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 24%-54%). The title Compound **367-1** was obtained as yellow solid.

Single-configuration Compound 367-1:

MS m/z (ESI): 581.4 [M+1]

Chiral HPLC analysis: retention time: 1.216 min; chromatographic column: Chiralcel OD-3 50 × 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.71 (m, 1H), 7.64 – 7.20 (m, 3H), 6.88 – 6.50 (m, 1H), 4.45 – 3.38 (m, 7H), 3.20 – 2.52 (m, 12H), 2.44 – 1.97 (m, 8H), 1.80 – 1.66 (m, 1H), 1.28 – 1.01 (m, 2H), 0.93 – 0.71 (m, 7H).

Step 5

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **368-1**

The crude product of Compound **367-1** (100.00 mg, 143.94 μmol, trifluoroacetate) was dissolved in methanol (2.0 mL). Triethylamine (29.13 mg, 287.88 μmol) and formaldehyde (116.81 mg, 1.44 mmol) were added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (27.14 mg, 431.82 μmol) was added, allowing for reacting at room temperature for 8.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%). The title Compound **368-1** (48 mg, 80.71 μmol, yield: 56.07%) was obtained as yellow solid.

Single-configuration Compound 368-1:

MS m/z (ESI):595.4 [M+1]

Chiral SFC: retention time: 1.047 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.73 (m, 1H), 7.66 – 7.22 (m, 3H), 6.89 – 6.53 (m, 1H), 4.43 – 3.44 (m, 6H), 3.30 – 2.52 (m, 10H), 2.43 – 2.04 (m, 13H), 1.79 – 1.67 (m, 1H), 1.23 – 0.67 (m, 9H).

Step 6

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **367-2**

Compound **366-2** (150.00 mg, 220.32 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (2.22 g, 19.47 mmol, 1.50 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **367-2** (130 mg), of which 100 mg of the crude product was directly used in the next step of reaction without purification. 30 mg of the crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%). The title Compound **367-2** was obtained as yellow solid.

Single-configuration Compound 367-2:

MS m/z (ESI): 581.4 [M+1]

Chiral HPLC analysis: retention time: 1.222 min; chromatographic column: Chiralcel OD-3 50 × 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.74 (m, 1H), 7.64 – 7.22 (m, 3H), 6.85 – 6.42 (m, 1H), 4.44 – 3.41 (m, 7H), 3.18 – 2.53 (m, 12H), 2.41 – 2.03 (m, 8H), 1.78 – 1.68 (m, 1H), 1.24 – 1.02 (m, 2H), 0.92 – 0.73 (m, 7H).

Step 7

(3*R*)-4-[5-fluoro-2-(1-fluoro-3-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoyl]-3-methylmorpholine **368-2**

The crude product of Compound **367-2** (100.00 mg, 143.94 μmol, trifluoroacetate) was dissolved in methanol (2.0 mL). Triethylamine (29.13 mg, 287.88 μmol) and formaldehyde (116.81 mg, 1.44 mmol) were added, and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (27.14 mg, 431.82 μmol) was added,

allowing for reacting at room temperature for 8.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%). The title Compound **368-2** (33 mg, 55.49 μmol, yield: 38.55%) was obtained as yellow solid.

Single-configuration Compound 368-2:

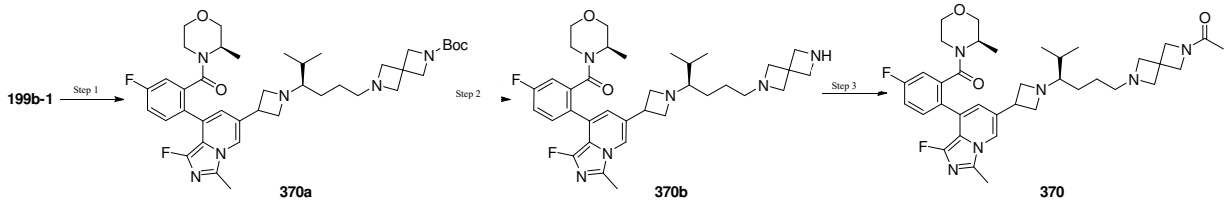
MS m/z (ESI):595.4 [M+1]

Chiral SFC: retention time: 1.05 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.71 (m, 1H), 7.64 – 7.23 (m, 3H), 6.88 – 6.44 (m, 1H), 4.38 – 3.44 (m, 6H), 3.25 (br s, 9H), 2.45 – 2.04 (m, 14H), 1.78 – 1.65 (m, 1H), 1.26 – 0.97 (m, 2H), 0.93 – 0.70 (m, 7H).

Example 370

1-{6-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl] -5-methylhexyl]-2,6-diazaspiro[3.3]heptan-2-yl}ethan-1-one **370**



Step 1

6-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,6-diazaspiro[3.3]heptan-2-tert-butyl carboxylate **370a**

Compound **199b-1** (120 mg, 222.79 μmol) and 2,6-diazaspiro[3.3]heptan-2-tert-butyl carboxylate (128.46 mg, 445.58 μmol, oxalate) were dissolved in methanol (2.0 mL), followed by the addition of triethylamine (45.09 mg, 445.58 μmol), and the mixture was stirred at room temperature for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (42.00 mg, 668.37 μmol) was added, allowing for reacting at room temperature for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title product **370a** (130 mg, 180.33 μmol, yield: 80.94%) as yellow oil.

MS m/z (ESI):721.5 [M+1]

Step 2

2-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,6-diazaspiro[3.3]heptane **370b**

Compound **370a** (130 mg, 180.33 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (15 mL), stirring for 0.5 hours and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **370b** (100 mg, 161.09 μmol, yield: 89.33%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 621.5 [M+1]

Step 3

1-{6-[(4*R*)-4-[3-(1-fluoro-8-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2,6-diazaspiro[3.3]heptan-2-yl}ethan-1-one **370**

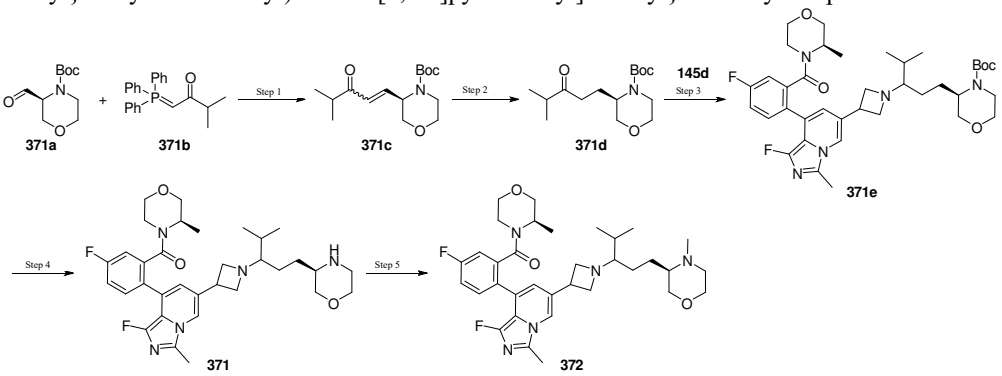
Triethylamine (48.90 mg, 483.27 μmol) and Compound **370b** (100 mg, 161.09 μmol) were dissolved in dichloromethane (3.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (32.89 mg, 322.18 μmol). The reaction mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia

water), elution gradient:30%-60%). The title Compound **370** (29.13 mg, 43.95 μmol, yield: 27.28%) was obtained as yellow solid.
MS m/z (ESI): 663.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.76 (m, 1H), 7.64 – 7.23 (m, 3H), 6.87 – 6.36 (m, 1H), 4.41 – 3.39 (m, 11H), 3.23 – 2.52 (m, 12H), 2.31 – 2.19 (m, 2H), 2.04 – 1.94 (m, 1H), 1.77 – 1.63 (m, 4H), 1.33 – 1.03 (m, 6H), 0.89 – 0.70 (m, 7H).

Examples 371 and 372

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **371**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*R*)-4-methylmorpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **372**



Step 1

(3*R*)-3-(4-methyl-3-oxo-1-ene-1-yl)morpholin-4-tert-butyl carboxylate **371c**

3-Methyl-1-(triphenylphosphinidene)but-2-one **371b** (3.22 g, 9.29 mmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of (3*S*)-3-formylmorpholin-4-tert-butyl carboxylate **371a**(1 g, 4.65 mmol), and the reaction mixture was stirred at 40°C for 48 hours. The reaction mixture was filtered and washed with, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **371c** (1 g, 3.53 mmol, yield: 75.96%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (dd, J = 4.9, 16.0 Hz, 1H), 6.14 (dd, J = 1.8, 16.0 Hz, 1H), 4.53 (s, 1H), 3.95 (d, J= 11.8 Hz, 1H), 3.80 (dd, J = 3.0, 11.4 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.42 – 3.36 (m, 1H), 3.10 – 3.00 (m, 1H), 2.98 – 2.85 (m, 1H), 1.41 (s, 9H), 1.02 (dd, J = 2.0, 6.9 Hz, 6H).

Step 2

(3*R*)-3-(4-methyl-3-oxopentyl)morpholin-4-tert-butyl carboxylate **371d**

Under the protection of nitrogen, Compound **371c** (1 g, 3.53 mmol) was dissolved in methanol (3.0 mL), followed by the addition of Pd/C(428.60 mg, 352.91 μmol, 10% content), and the reaction mixture was stirred at 30°C for 12 hours under a hydrogen atmosphere (20 PSI). The reaction mixture was filtered through diatomite, and the filtrate was concentrated under a reduced pressure, to obtain the title Compound **371d** (1 g, 3.50 mmol, yield: 99.39%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 – 3.71 (m, 2H), 3.69 – 3.54 (m, 2H), 3.42 – 3.38 (m, 1H), 3.30 – 3.23 (m, 1H), 3.06 – 2.91 (m, 1H), 2.60 – 2.54 (m, 1H), 2.48 – 2.34 (m, 2H), 1.98 – 1.85 (m, 1H), 1.76 – 1.63 (m, 1H), 1.40 (s, 9H), 1.00 (dd, J = 2.4, 7.2 Hz, 6H).

Step 3

(3*R*)-3-{3-[3-(1-fluoro-8-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl}morpholin-4-tert-butyl carboxylate **371e**

Compound **145d** (809 mg, 1.90 mmol) and Compound **371d** (1.08 g, 3.79 mmol) were dissolved in methanol (10.0 mL), followed by the addition of $ZnCl_2$ (517.11 mg, 3.79 mmol), and the mixture was stirred at 25°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (357.64 mg, 5.69 mmol), allowing for reacting at 25°C for 12 hours under the protection of nitrogen. Water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 47%-77%), to obtain the title Compound **371e** (600 mg, 862.27 μmol, yield: 45.45%).
MS m/z (ESI): 696.0 [M+1]

Step 4

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **371**

Compound **371e** (123 mg, 176.77 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product was dissolved in dichloromethane (5 mL), followed by adding water (5 mL) and regulating to PH > 7 with 10% aqueous NaOH solution. The mixture was extracted with dichloromethane (10 mL x 3), and the organic phases were combined and concentrated under a reduced pressure. The resulting crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **371** (75.19 mg, 126.22 μmol, yield: 71.4%) as yellow solid.

MS m/z (ESI):596.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, J = 12.4 Hz, 1H), 7.70 – 7.50 (m, 1H), 7.43 – 7.07 (m, 2H), 6.96 – 6.53 (m, 1H), 4.60 – 4.01 (m, 1H), 3.89 – 3.56 (m, 7H), 3.54 – 3.44 (m, 1H), 3.33 (s, 2H), 3.29 – 3.21 (m, 2H), 3.15 (t, J = 10.4 Hz, 1H), 3.02 – 2.80 (m, 3H), 2.70 (s, 1H), 2.62 (s, 3H), 2.21 (s, 2H), 1.92 – 1.80 (m, 1H), 1.61 – 1.46 (m, 1H), 1.39 (s, 3H), 1.34 – 1.26 (m, 1H), 1.24 – 1.15 (m, 1H), 1.00 – 0.88 (m, 6H), 0.83 (s, 1H).

Step 5

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*R*)-4-methylmorpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **372**

Compound **371** (128 mg, 214.87 μmol) was dissolved in methanol (5.0 mL), followed by the addition of acetic acid (38.71 mg, 644.60 μmol) and formaldehyde (26.15 mg, 322.30 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (27.00 mg, 429.73 μmol) was added, allowing for reacting at 25°C for 3.0 hours under the protection of nitrogen. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-63%), to obtain the title Compound **372** (76.95 mg, 126.20 μmol, yield: 58.73%).

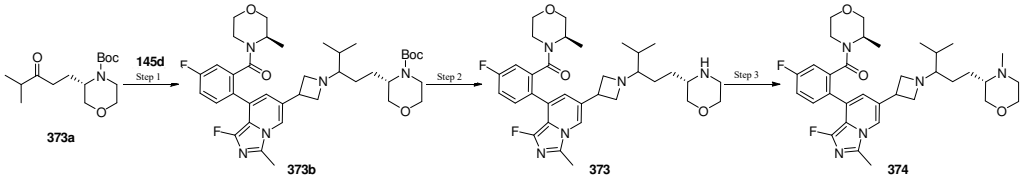
MS m/z (ESI):610.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 13.6 Hz, 1H), 7.64 – 7.50 (m, 1H), 7.38 – 7.16 (m, 2H), 6.87 – 6.60 (m, 1H), 3.83 – 3.53 (m, 8H), 3.33 – 3.18 (m, 8H), 2.70 (d, J = 12.0 Hz, 1H), 2.60 (s, 3H), 2.37 – 2.27 (m, 4H), 2.21 (s, 1H), 2.13 – 2.02 (m, 1H), 1.90 – 1.78 (m, 1H), 1.77 – 1.64 (m, 1H), 1.50 – 1.24 (m, 4H), 1.21 – 1.11 (m, 1H), 0.98 – 0.87 (m, 6H), 0.81 (d, J = 4.4 Hz, 1H).

Examples 373 and 374

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **373**

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*S*)-4-methylmorpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **374**



Step 1

(3*S*)-3-{3-[3-(1-fluoro-8-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl}morpholin-4-tert-butyl carboxylate **373b**

Compound **145d** (250 mg, 586.22 μmol) and Compound **373a**(167.30 mg, 586.22 μmol, synthesized according to the synthesis route of Compound **371d** by using (3*R*)-3-formylmorpholin-4-tert-butyl carboxylate as a starting material to replace (3*S*)-3-formylmorpholin-4-tert-butyl carboxylate **371a**) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (159.80 mg, 1.17 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by the addition of sodium cyanoborohydride (110.52 mg, 1.76 mmol), allowing for reacting at 50°C for 11 hours under the protection of nitrogen. A saturated aqueous sodium carbonate solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **373b** (370 mg, 531.73 μmol, yield: 90.70%).

MS m/z (ESI): 696.3 [M+1]

Step 2

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **373**

Compound **373b** (60 mg, 86.23 μmol) was dissolved in dichloromethane (6.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The crude product was dissolved in dichloromethane (5 mL), followed by adding water (5 mL) and regulating to PH > 7 with 10% aqueous NaOH solution. The mixture was extracted with dichloromethane (10 mL x 3), and the organic phases were combined and concentrated under a reduced pressure. The resulting crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **373** (17.87 mg, 30.00 μmol, yield: 34.79%) as yellow solid.

MS m/z (ESI):596.2 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 13.6 Hz, 1H), 7.66 – 7.49 (m, 1H), 7.40 – 7.16 (m, 2H), 6.89 – 6.59 (m, 1H), 4.64 – 4.01 (m, 2H), 3.83 – 3.54 (m, 7H), 3.48 (m, 1H), 3.28 – 3.10 (m, 4H), 3.03 – 2.79 (m, 3H), 2.74 – 2.65 (m, 1H), 2.60 (s, 3H), 2.20 (s, 1H), 1.90 – 1.76 (m, 1H), 1.52 – 1.15 (m, 6H), 1.04 – 0.50 (m, 8H).

Step 3

(3*R*)-4-{5-fluoro-2-[1-fluoro-3-methyl-6-(1-{4-methyl-1-[(3*S*)-4-methylmorpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]benzoyl}-3-methylmorpholine **374**

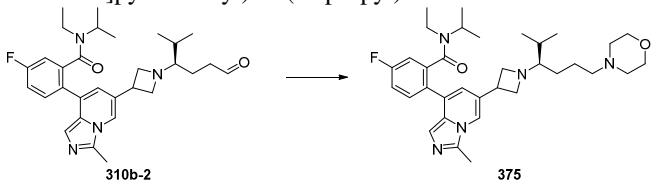
Compound **373** (54 mg, 90.65 μmol) was dissolved in methanol (5.0 mL), followed by the addition of formaldehyde (13.61 mg, 453.23 μmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (17.09 mg, 271.94 μmol) was added, allowing for reacting at 25°C for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-630), to obtain the title Compound **374** (28.64 mg, 46.97 μmol, yield: 51.82%).

MS m/z (ESI):610.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.39 (m, 2H), 7.27 – 7.08 (m, 2H), 6.83 – 6.58 (m, 1H), 4.64 – 4.13 (m, 1H), 3.84 – 3.51 (m, 8H), 3.40 – 3.23 (m, 2H), 3.20 – 2.93 (m, 4H), 2.84 – 2.65 (m, 2H), 2.62 (s, 3H), 2.38 – 2.28 (m, 4H), 2.11 – 2.02 (m, 2H), 1.88 – 1.73 (m, 2H), 1.46 – 1.13 (m, 5H), 0.96 – 0.88 (m, 6H), 0.85 – 0.59 (m, 1H).

Example 375

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(morpholin-4-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **375**



310b-2 375

Compound **310b-2** (121 mg, 238.82 μmol) and morpholine (24.97 mg, 286.59 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (43.03 mg, 716.47 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (30.02 mg, 477.64 μmol) was added, allowing for reacting at 25°C for 13.0 hours under the protection of nitrogen. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title Compound **375** (37.24 mg, 64.45 μmol, yield: 26.99%) as faint yellow solid.

MS m/z (ESI):578.5[M+1]

Chiral SFC: retention time: 1.073 min; chromatographic column: Chiralcel OD-3 50 × 4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.89 (m, 1H), 7.76 – 7.68 (m, 1H), 7.38 – 7.30 (m, 1H), 7.28 – 7.20 (m, 1H), 7.16 – 7.11 (m, 1H), 6.95 – 6.84 (m, 1H), 3.83 – 3.76 (m, 1H), 3.75 – 3.62 (m, 6H), 3.56 (td, J = 6.4, 12.8 Hz, 1H), 3.43 (qd, J = 6.4, 13.2 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.09 – 2.95 (m, 1H), 2.66 (s, 3H), 2.52 – 2.42 (m, 4H), 2.36 (q, J = 7.6 Hz, 2H), 2.30 – 2.22 (m, 1H), 1.94 – 1.79 (m, 1H), 1.71 – 1.52 (m, 2H), 1.48 – 1.37 (m, 1H), 1.36 – 1.25 (m, 1H), 1.21 – 1.09 (m, 1H), 1.01 – 0.87 (m, 12H), 0.80 (t, J = 7.0 Hz, 1H), 0.30 (d, J = 6.4 Hz, 2H).

Example 378

2-(6-{1-[(3*R*)-6-{3-acetyl-3,8-diazabicyclo[3.2.1]oct-8-yl}-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-

methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **378**

Step 1

8-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-3,8-diazabicyclo[3.2.1]octan-3-tert-butyl carboxylate **378a**

Compound **310b-2** (180 mg, 355.27 μmol) and 3,8-diazabicyclo[3.2.1]octan-3-tert-butyl carboxylate (150.84 mg, 710.55 μmol) were dissolved in methanol (4.0 mL), followed by the addition of acetic acid (21.33 mg, 355.27 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (66.98 mg, 1.07 mmol) was added, allowing for reacting at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **378a** (200 mg, 284.52 μmol, yield: 80.08%) as faint yellow solid.

MS m/z (ESI):703.8 [M+1]

Step 2

2-(6-{1-[(3*R*)-6-{3,8-diazabicyclo[3.2.1]oct-8-yl}-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **378b**

Compound **378a** (200 mg, 284.52 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, and then dissolved by adding DCM (10 mL), followed by adding a 10% aqueous sodium hydroxide solution (15 mL), stirring for 0.5 hours and extracting with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **378b** (170 mg, 282.01 μmol, yield: 99.12%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 503.2 [M+1]

Step 3

2-(6-{1-[(3*R*)-6-{3-acetyl-3,8-diazabicyclo[3.2.1]oct-8-yl}-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **378**

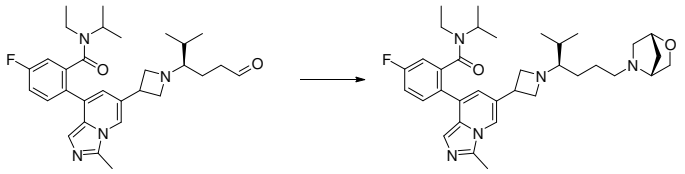
Triethylamine (85.61 mg, 846.02 μmol) and Compound **378b** (170 mg, 282.01 μmol) were dissolved in dichloromethane (4.0 mL), and cooled to 5°C, followed by the addition of acetic anhydride (57.58 mg, 564.01 μmol). The reaction mixture was stirred at room temperature for 1.0 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:30%-60%). The title Compound **378** (65.61 mg, 101.74 μmol, yield: 36.08%) was obtained as yellow solid.

MS m/z (ESI): 645.9 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.81 (m, 1H), 7.78 – 7.51 (m, 1H), 7.50 – 7.13 (m, 2H), 7.13 – 6.93 (m, 1H), 6.90 – 6.65 (m, 1H), 4.36 – 3.83 (m, 1H), 3.65 – 3.34 (m, 5H), 3.29 – 2.62 (m, 8H), 2.62 – 2.57 (m, 3H), 2.35 – 2.13 (m, 2H), 2.10 – 1.99 (m, 1H), 1.99 – 1.86 (m, 3H), 1.83 – 1.63 (m, 3H), 1.53 – 1.19 (m, 6H), 1.09 – 0.69 (m, 13H), 0.30 – 0.23 (m, 2H).

Example 379

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **379**



Compound **310b-2** (90 mg, 177.64 μmol) and (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (28.90 mg, 213.16 μmol, hydrochloride) were dissolved in methanol (2.0 mL), followed by the addition of triethylamine (53.92 mg, 532.91 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (33.49 mg, 532.91 μmol) was added, allowing for reacting at 25℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%). The title Compound **379** (31.38 mg, 53.21 μmol, yield: 29.95%) was obtained as yellow solid.

MS m/z (ESI):590.7[M+1]

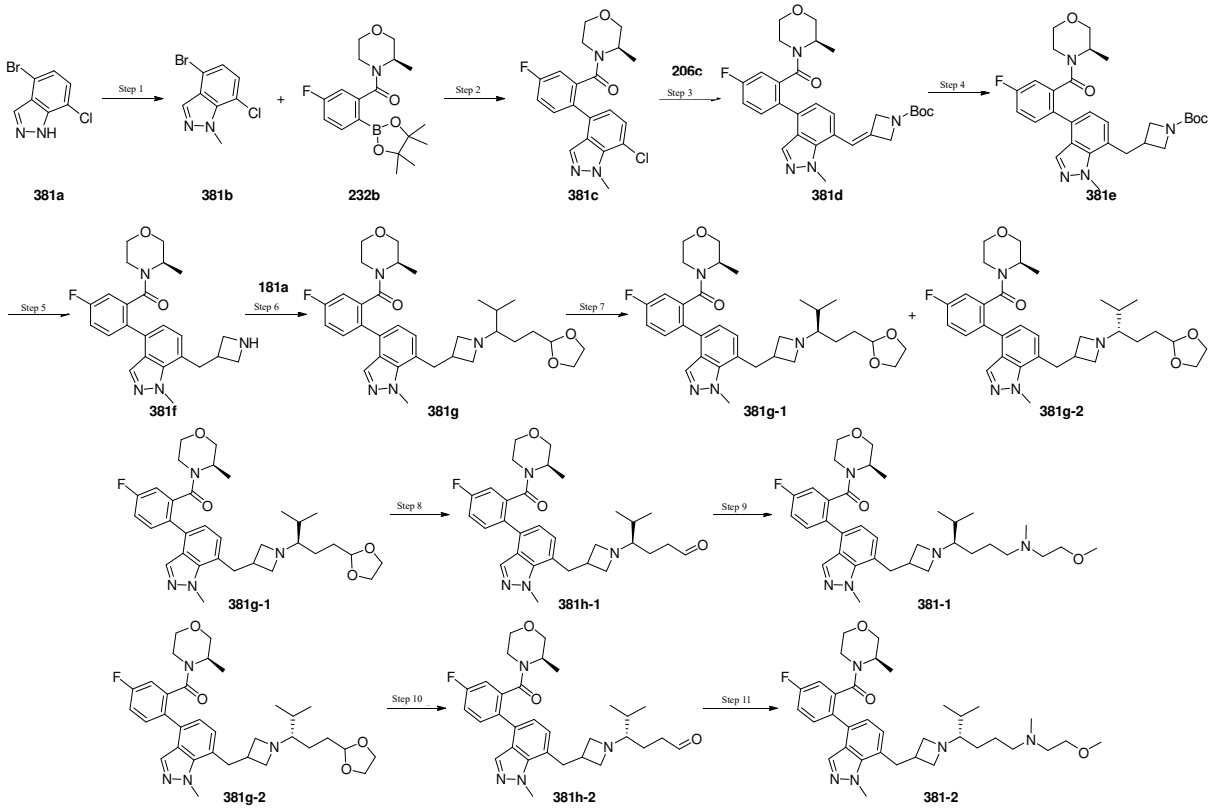
Chiral SFC: retention time: 1.160 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.63 (m, 1H), 7.42 – 7.26 (m, 2H), 7.08 – 6.99 (m, 1H), 6.87 – 6.70 (m, 1H), 4.27 (s, 1H), 3.78 (d, J = 7.2 Hz, 1H), 3.60 – 3.34 (m, 6H), 3.31 – 3.24 (m, 1H), 3.18 – 3.02 (m, 2H), 2.97 – 2.86 (m, 1H), 2.72 (d, J = 10.0 Hz, 1H), 2.59 (s, 3H), 2.49 – 2.29 (m, 3H), 2.03 (s, 1H), 1.77 – 1.63 (m, 2H), 1.55 – 1.46 (m, 1H), 1.45 – 1.01 (m, 5H), 0.92 – 0.71 (m, 12H), 0.27 (d, J = 6.5 Hz, 2H).

Examples 381-1 and 381-2

[(4*R*)-4-{3-[(4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexyl](2-methoxyethyl)methylamine **381-1**

[(4*S*)-4-{3-[(4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexyl](2-methoxyethyl)methylamine **381-2**



Step 1

4-bromo-7-chloro-1-methyl-1*H*-indazole **381b**

4-Bromo-7-chloro-1*H*-indazole **381a** (10 g, 43.20 mmol) was dissolved in *N,N*-dimethylformamide (100 mL), and cooled to 0°C. NaH (2.07 g, 51.84 mmol, 60% purity) was added, and the mixture was stirred at 0°C to allow for reacting for 0.5 hours. Iodomethane (7.36 g, 51.84 mmol) was added, and the mixture was stirred at room temperature to allow for reacting for 1.0 hour. A saturated aqueous ammonium chloride solution (30 mL) was slowly added at 0°C, and the mixture then extracted with ethyl acetate (60 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **381b** (7.47 g, 30.43 mmol, yield: 70.43%) as faint yellow solid.
MS m/z (ESI): 246.8 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.42 – 7.27 (m, 2H), 4.31 (s, 3H).

Step 2

7-chloro-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **381c**

Compound **381b** (4 g, 8.15 mmol), Compound **232b**(2.99 g, 8.15 mmol) and potassium phosphate (5.19 g, 24.44 mmol) were dissolved in dioxane (60 mL) and water (6.0 mL). Pd(dtbpf)Cl_2 (530.95 mg, 814.65 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **381c** (3 g, 7.74 mmol, yield: 94.95%).
MS m/z (ESI): 388.1 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.40 (s, 1H), 7.24 – 7.06 (m, 2H), 6.68 (s, 1H), 4.63 – 4.44 (m, 1H), 4.35 – 4.26 (m, 2H), 3.95 (br d, J = 6.0 Hz, 2H), 3.67 (s, 3H), 3.31 – 2.99 (m, 2H), 2.61 (s, 3H), 1.66 (br s, 3H), 1.46 (s, 9H), 1.31 – 1.23 (m, 2H).

Step 3

3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methylene]azacyclobutan-1-tert-butyl carboxylate **381d**

Compound **381c** (500 mg, 1.29 mmol), 3-[(tetramethyl-1,3,2-dioxaboran-2-yl)methylene]azacyclobutan-1-tert-butyl carboxylate **206c** (380.55 mg, 1.29 mmol) and potassium phosphate (820.97 mg, 3.87 mmol) were dissolved in dioxane (5 mL) and water (1 mL). Pd(dtbpf)Cl_2 (84.02 mg, 128.92 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **381d** (518 mg, 995.02 μmol, yield: 77.18%).
MS m/z (ESI): 521.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.80 (m, 1H), 7.62 – 7.49 (m, 1H), 7.27 – 7.15 (m, 3H), 7.14 – 7.05 (m, 1H), 7.04 – 6.92 (m, 1H), 4.85 – 4.64 (m, 4H), 4.38 – 4.30 (m, 3H), 4.18 – 4.02 (m, 1H), 3.68 – 3.34 (m, 2H), 3.24 – 3.11 (m, 1H), 3.10 – 2.93 (m, 1H), 2.89 – 2.77 (m, 1H), 2.58 – 2.27 (m, 1H), 1.61 (s, 3H), 1.49 (s, 9H).

Step 4

3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-tert-butyl carboxylate **381e**

Compound **381d** (418 mg, 802.93 μmol) was dissolved in methanol (10 mL), followed by the addition of Rh/Al_2O_3 (32.90 mg, 160.59 μmol) under a nitrogen atmosphere. The reaction atmosphere was substituted with a nitrogen atmosphere (15 psi), and the mixture was stirred at room temperature for 3.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **381e** (419 mg, 801.75 μmol, yield: 99.85%).
MS m/z (ESI): 523.2 [M+1]

Step 5

7-[(azacyclobutan-3-yl)methyl]-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **381f**

Compound **381e** (300 mg, 574.04 μmol) was dissolved in methane dioxide (7.3 mL), followed by the addition of trifluoroacetic acid (2.57 g, 22.55 mmol, 1.74 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (5.0 mL) and water (5.0 mL), regulated to PH > 7 by adding a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **381f** (242 mg, 572.79 μmol, yield: 99.78%). The crude product was directly used in the next step of reaction without

purification.
MS m/z (ESI): 423.1 [M+1]

Step 6

7-({1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **381g**

Compound **381f** (242 mg, 572.79 μmol) and Compound **181a**(197.29 mg, 1.15 mmol) were dissolved in methanol (40 mL). Zinc chloride (156.14 mg, 1.15 mmol) was added, and the mixture was stirred at room temperature for 30 min. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (107.99 mg, 1.72 mmol) and stirring at room temperature for 2.0 hours. Water (20 mL) was added, and the mixture was extracted with dichloromethane (10 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **381g** (291 mg, 502.84 μmol, yield: 87.79%) as yellow solid.
MS m/z (ESI): 579.4[M+1]

Step 7

7-({1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **381g-1**

7-({1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazole **381g-2**

Compound **381g** (291 mg, 502.84 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: CO_2-MeOH (0.1% ammonia water); elution gradient: 32%), to obtain the title Compounds **381g-1** (97 mg, 167.61 μmol, yield: 33.3%) and **381g-2** (87 mg, 150.33 μmol, yield: 29.9%).

Single-configuration Compound 381g-1:
MS m/z (ESI):579.4 [M+1]
Chiral HPLC analysis: retention time: 1.407 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 381g-2:
MS m/z (ESI):579.4 [M+1]
Chiral HPLC analysis: retention time: 1.544 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Step 8

(4*R*)-4-{3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexanal **381h-1**

Compound **381g-1** (97 mg, 167.61 μmol) was dissolved in acetonitrile (5.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 5.0 mL). The mixture was stirred at 50℃ to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with dichloromethane (5.0 mL) and water (5.0 mL), regulated to pH ≥ 7 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **381h-1** (89.62 mg, 167.62 μmol, yield: 100%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 381h-1:
MS m/z (ESI): 535.3 [M+1]

Step 9

[(4*R*)-4-{3-[(4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexyl](2-methoxyethyl)methylamine **381-1**

The crude product of Compound **381h-1** (89.62 mg, 167.62 μmol) and 2-methoxy-*N*-methylethylamine (17.93 mg, 201.14 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (20.13 mg, 335.24 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (31.60 mg, 502.86 μmol) was added, allowing for reacting at 50℃ for 2.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 4%-34%). The title Compound **381-1** (11.86 mg, 19.51 μmol, yield: 11.64%) was obtained.

Single-configuration Compound 381-1:
MS m/z (ESI):608.5 [M+1]

Chiral SFC: retention time: 0.827 min; chromatographic column: Chiralcel OJ-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 8.34 – 8.28 (m, 1H), 7.72 – 7.56 (m, 1H), 7.43 – 7.26 (m, 1H), 7.18 – 7.08 (m, 1H), 7.07 – 6.92 (m, 2H), 6.91 – 6.73 (m, 1H), 4.29 – 3.94 (m, 4H), 3.89 – 3.66 (m, 2H), 3.58 – 3.44 (m, 2H), 3.43 – 3.37 (m, 2H), 3.35 – 3.21 (m, 3H), 3.18 – 3.11 (m, 3H), 3.11 – 3.03 (m, 2H), 3.02 – 2.88 (m, 2H), 2.86 – 2.78 (m, 2H), 2.73 – 2.56 (m, 4H), 2.46 – 2.37 (m, 3H), 2.36 – 2.08 (m, 1H), 1.88 – 1.70 (m, 1H), 1.49 (s, 2H), 1.39 – 1.17 (m, 2H), 1.13 – 0.93 (m, 1H), 0.89 – 0.65 (m, 7H), 0.41 - -0.07 (m, 1H).

Step 10

(4*S*)-4-{3-[(4-{4-fluoro-2-[(3*R*)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexanal **381h-2**

Compound **381g-2** (87 mg, 150.33 μmol) was dissolved in acetonitrile (5.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 5.0 mL). The mixture was stirred at 50°C to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, diluted with dichloromethane (5.0 mL) and water (5.0 mL), regulated to pH ≥ 7 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **381h-2** (80.38 mg, 150.34 μmol, yield: 100%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 381h-2:

MS m/z (ESI): 535.2 [M+1]

Step 11

[(4*S*)-4-{3-[(4-{4-fluoro-2-[(3R)-3-methylmorpholin-4-carbonyl]phenyl}-1-methyl-1*H*-indazol-7-yl)methyl]azacyclobutan-1-yl}-5-methylhexyl](2-methoxyethyl)methylamine **381-2**

The crude product of Compound **381h-2** (80.38 mg, 150.34 μmol) and 2-methoxy-*N*-methylethylamine (16.08 mg, 180.41 μmol) were dissolved in methanol (5 mL), followed by the addition of acetic acid (18.06 mg, 300.68 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (28.34 mg, 451.01 μmol) was added, allowing for reacting at 50°C for 2.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 3%-33%). The title Compound **381-2** (10.08 mg, 16.58 μmol, yield: 11.03%) was obtained.

Single-configuration Compound 381-2:

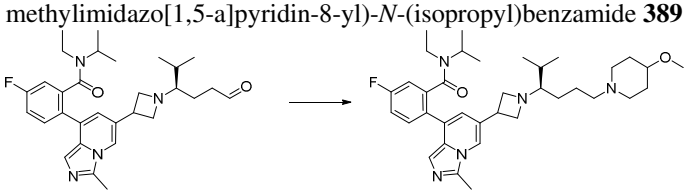
MS m/z (ESI):608.5 [M+1]

Chiral SFC: retention time: 1.250 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.64 – 7.53 (m, 1H), 7.36 – 7.22 (m, 1H), 7.11 – 7.01 (m, 1H), 7.01 – 6.87 (m, 2H), 6.84 – 6.69 (m, 1H), 4.05 (d, J = 4.0 Hz, 4H), 3.73 – 3.54 (m, 2H), 3.34 – 3.28 (m, 3H), 3.27 – 3.11 (m, 4H), 3.07 (s, 3H), 3.03 – 2.91 (m, 2H), 2.90 – 2.72 (m, 2H), 2.71 – 2.53 (m, 3H), 2.50 – 2.35 (m, 3H), 2.30 – 2.20 (m, 3H), 2.17 – 2.05 (m, 1H), 1.75 – 1.59 (m, 1H), 1.38 (s, 2H), 1.28 – 1.09 (m, 2H), 1.07 – 0.89 (m, 1H), 0.79 – 0.60 (m, 7H), 0.31 - -0.12 (m, 1H).

Example 389

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **389**



310b-2 **389**

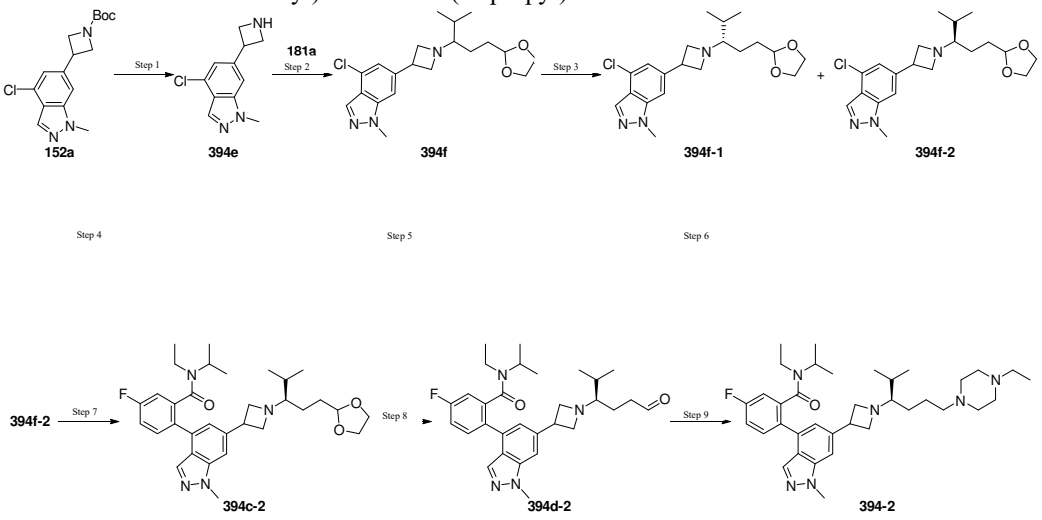
Compound **310b-2** (90 mg, 177.64 μmol) and 4-methoxypiperidine (40.92 mg, 355.27 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (10.67 mg, 177.64 μmol), and the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (33.49 mg, 532.91 μmol) was added, allowing for reacting at 25°C for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution

gradient: 0%-30%). The title Compound **389** (15.9 mg, 26.25 μmol, yield: 14.77%) was obtained.
MS m/z (ESI):606.9[M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1.7H), 8.01 – 7.87 (m, 1H), 7.76 – 7.62 (m, 1H), 7.45 – 7.27 (m, 2H), 7.08 – 6.99 (m, 1H), 6.87 – 6.69 (m, 1H), 3.63 – 3.57 (m, 2H), 3.55 – 3.50 (m, 1H), 3.48 – 3.41 (m, 1H), 3.35 – 3.26 (m, 1H), 3.23 – 3.11 (m, 6H), 2.98 – 2.86 (m, 1H), 2.78 – 2.69 (m, 2H), 2.59 (s, 3H), 2.35 (t, J = 7.2 Hz, 2H), 2.25 – 2.06 (m, 3H), 1.88 – 1.66 (m, 3H), 1.55 – 1.36 (m, 4H), 1.31 – 0.98 (m, 3H), 0.95 – 0.68 (m, 12H), 0.32 – 0.23 (m, 2H).

Examples 394-1 and 394-2

N-ethyl-2-(6-{1-[(3*S*)-6-(4-ethylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluoro-*N*-(isopropyl)benzamide **394-1**

N-ethyl-2-(6-{1-[(3*R*)-6-(4-ethylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluoro-*N*-(isopropyl)benzamide **394-2**



Step 1

6-(azacyclobutan-3-yl)-4-chloro-1-methyl-1*H*-indazole **394e**

Compound **152a** (500 mg, 1.55 mmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 15 min. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (20 mL), regulating to pH = 11 with a 10% aqueous sodium hydroxide solution, and extracting with dichloromethane (40 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **394e** (350 mg, 1.58 mmol, yield: 101.6%) as yellow oil. The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 221.8 [M+1]

Step 2

4-chloro-6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **394f**

Compound **394e** (340 mg, 1.53 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (343.38 mg, 1.99 mmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$(418.08 mg, 3.07 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (289.14 mg, 4.60 mmol) and stirring at 50°C for 8.0 hour. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **394f** (350 mg, 926.15 μmol, yield: 60.39%) as yellow oil.
MS m/z (ESI): 378.2 [M+1]

Step 3

4-chloro-6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **394f-1**
4-chloro-6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **394f-2**

Compound **394f** (350 mg, 926.15 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol; elution gradient: 35%), to obtain the title Compounds **394f-1** (145 mg, 383.69 μmol, yield: 41.43%) and **394f-2** (145 mg, 383.69 μmol, yield: 41.43%).

Single-configuration Compound 394f-1:
MS m/z (ESI): 378.0 [M+1]
Chiral HPLC analysis: retention time: 1.375 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.
Single-configuration Compound 394f-2:
MS m/z (ESI): 378.0 [M+1]
Chiral HPLC analysis: retention time: 1.534 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 4

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **394c-1**

Compound **394f-1** (145 mg, 383.69 μmol), Compound **4c**(257.24 mg, 767.38 μmol) and potassium phosphate (244.33 mg, 1.15 mmol) were dissolved in dioxane (2.0 mL) and water (0.4 mL). Pd(dtbpf)Cl_2 (25.01 mg, 38.37 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **394c-1** (150 mg, 272.38 μmol, yield: 70.99%) as brown solid.
MS m/z (ESI): 551.3[M+1]
Chiral HPLC analysis: retention time: 1.122 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 5

N-ethyl-5-fluoro-2-{1-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **394d-1**

Compound **394c-1** (150 mg, 272.38 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 11 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **394d-1** (140 mg). The crude product was directly used in the next step of reaction without purification.
Single-configuration Compound 394d-1:
MS m/z (ESI): 507.4 [M+1]

Step 6

N-ethyl-2-(6-{1-[(3*S*)-6-(4-ethylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluoro-*N*-(isopropyl)benzamide **394-1**

The crude product of Compound **394d-1** (140 mg, 276.32 μmol) and 1-ethylpiperazine (63.11 mg, 552.65 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (24.89 mg, 414.48 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (52.09 mg, 828.97 μmol) was added, allowing for reacting at room temperature for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The title Compound **394-1** (28.88 mg, 47.75 μmol, yield: 17.28%) was obtained.
Single-configuration Compound 394-1:
MS m/z (ESI):605.3 [M+1]
Chiral SFC: retention time: 1.146 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.59 – 7.52 (m, 1H), 7.27 – 7.08 (m, 4H), 4.10 (s, 3H), 3.92 – 3.80 (m, 3H), 3.52 – 3.38 (m, 2H), 3.29 – 3.18 (m, 2H), 2.86 – 2.77 (m, 1H), 2.56 – 2.48 (m, 4H), 2.45 – 2.40 (m, 3H), 2.37 – 2.30 (m, 3H), 2.18 – 2.09 (m, 1H), 1.89 – 1.77 (m, 1H), 1.63 – 1.51 (m, 2H), 1.41 – 1.30 (m, 2H), 1.13 – 1.05 (m, 4H), 0.99 – 0.78 (m, 13H), 0.74 – 0.68 (m, 1H), 0.09 – 0.03 (m, 2H).

Step 7

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **394c-2**

Compound **394f-2** (145 mg, 383.69 μmol), Compound **4c**(257.24 mg, 767.38 μmol) and potassium phosphate (244.33

mg, 1.15 mmol) were dissolved in dioxane (2.0 mL) and water (0.4 mL). Pd(dtbpf)Cl_2 (25.01 mg, 38.37 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **394c-2** (150 mg, 272.38 μmol, yield: 70.99%) as brown solid.

MS m/z (ESI): 551.3[M+1]

Chiral HPLC analysis: retention time: 1.102 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 8

N-ethyl-5-fluoro-2-{1-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl]-1*H*-indazol-4-yl}-*N*-(isopropyl)benzamide **394d-2**

Compound **394c-2** (150 mg, 272.38 μmol) was dissolved in acetonitrile (1.5 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.5 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 11 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **394d-2** (140 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 394d-2:

MS m/z (ESI): 507.3 [M+1]

Step 9

N-ethyl-2-(6-{1-[(3*R*)-6-(4-ethylpiperazin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-5-fluoro-*N*-(isopropyl)benzamide **394-2**

The crude product of Compound **394d-2** (140 mg, 276.32 μmol) and 1-ethylpiperazine (63.11 mg, 552.65 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (24.89 mg, 414.48 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (17.36 mg, 276.32 μmol) was added, allowing for reacting at room temperature for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The title Compound **394-2** (44.93 mg, 74.28 μmol, yield: 26.88%) was obtained.

Single-configuration Compound 394-2:

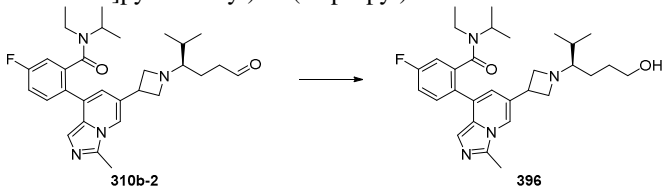
MS m/z (ESI):605.3 [M+1]

Chiral SFC: retention time: 1.033 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.60 – 7.49 (m, 1H), 7.26 – 7.02 (m, 4H), 4.10 (s, 3H), 3.94 – 3.78 (m, 3H), 3.51 – 3.36 (m, 2H), 3.31 – 3.17 (m, 2H), 2.86 – 2.76 (m, 1H), 2.58 – 2.49 (m, 4H), 2.46 – 2.41 (m, 3H), 2.37 – 2.28 (m, 3H), 2.18 – 2.10 (m, 1H), 1.89 – 1.76 (m, 1H), 1.63 – 1.49 (m, 2H), 1.42 – 1.30 (m, 2H), 1.14 – 1.02 (m, 4H), 0.96 – 0.77 (m, 13H), 0.75 – 0.68 (m, 1H), 0.08 – 0.03 (m, 2H).

Example 396

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-hydroxyl-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **396**



Compound **310b-2** (90 mg, 177.64 μmol) was dissolved in methanol (2.0 mL), followed by the addition of acetic acid (10.67 mg, 177.64 μmol), and the mixture was stirred at 50°C for 0.5 hours. Sodium cyanoborohydride (33.49 mg, 532.91 μmol) was added, allowing for reacting at 50℃ for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium carbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC

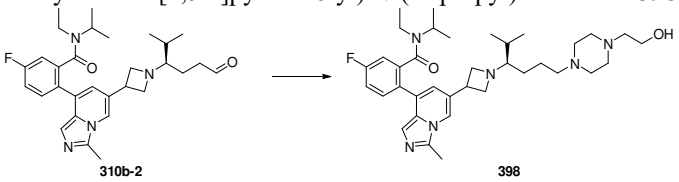
(mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title Compound **396** (22.76 mg, 44.74 μmol, yield: 25.19%) as yellow solid.

MS m/z (ESI):509.4[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.89 (m, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.06 – 7.01 (m, 1H), 6.84 – 6.69 (m, 1H), 4.41 – 4.21 (m, 1H), 3.60 – 3.36 (m, 5H), 3.22 – 2.72 (m, 4H), 2.62 – 2.54 (m, 3H), 2.06 – 1.97 (m, 1H), 1.77 – 1.65 (m, 1H), 1.52 – 1.39 (m, 2H), 1.32 – 1.00 (m, 3H), 0.93 – 0.71 (m, 13H), 0.31 – 0.25 (m, 2H).

Example 398

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **398**



310b-2 398

Compound **310b-2** (180 mg, 355.27 μmol) and 2-piperazin-1-ylethanol (92.50 mg, 710.55 μmol) were dissolved in methanol (4.0 mL), followed by the addition of acetic acid (21.33 mg, 355.27 μmol), and the mixture was stirred at room temperature for 0.5 hours. Sodium cyanoborohydride (66.98 mg, 1.07 mmol) was added, allowing for reacting 25℃ for 15.0 hours under the protection of nitrogen. A saturated aqueous sodium carbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-66%), to obtain the title Compound **398** (85.12 mg, 137.10 μmol, yield: 38.59%) as yellow solid.

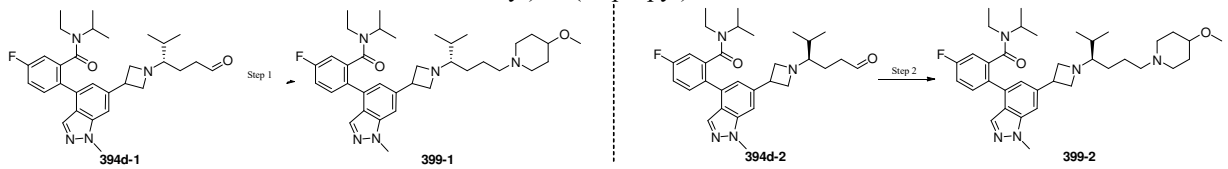
MS m/z (ESI):621.8[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.86 (m, 1H), 7.73 – 7.61 (m, 1H), 7.43 – 7.26 (m, 2H), 7.10 – 6.93 (m, 1H), 6.86 – 6.67 (m, 1H), 4.35 – 4.24 (m, 1H), 3.58 – 3.41 (m, 6H), 3.19 – 2.77 (m, 4H), 2.61 – 2.55 (m, 3H), 2.41 – 2.26 (m, 9H), 2.23 – 2.18 (m, 2H), 2.06 – 1.98 (m, 1H), 1.77 – 1.66 (m, 1H), 1.50 – 1.36 (m, 2H), 1.32 – 1.02 (m, 3H), 0.95 – 0.68 (m, 13H), 0.30 – 0.25 (m, 2H).

Examples 399-1 and 399-2

N-ethyl-5-fluoro-2-(6-{1-[(3*S*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **399-1**

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **399-2**



394d-1 399-1 394d-2 399-2

Step 1

N-ethyl-5-fluoro-2-(6-{1-[(3*S*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)- *N*-(isopropyl)benzamide **399-1**

Compound **394d-1** (200 mg, 276.32 μmol) and 4-methoxypiperidine (90.93 mg, 789.49 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (47.41 mg, 789.49 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (74.42 mg, 1.18 mmol) was added, allowing for reacting at room temperature for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 50%-80%), to obtain the title Compound **399-1** (61.76 mg, 101.94 μmol, yield: 25.82%) as yellow solid.

Single-configuration Compound 399-1:

MS m/z (ESI):606.3 [M+1]

Chiral SFC: retention time: 1.162 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.77 (m, 1H), 7.62 – 7.56 (m, 1H), 7.55 – 7.49 (m, 1H), 7.42 – 7.35 (m, 1H), 7.33 – 7.24 (m, 1H), 7.15 – 7.02 (m, 1H), 4.04 (s, 3H), 3.70 – 3.59 (m, 3H), 3.27 – 3.05 (m, 7H), 2.88 – 2.76 (m, 1H), 2.66 – 2.59 (m, 2H), 2.23 – 2.17 (m, 2H), 2.05 – 1.93 (m, 3H), 1.82 – 1.70 (m, 3H), 1.47 – 1.31 (m, 4H), 1.28 – 1.16 (m, 2H), 1.04 – 0.77 (m, 10H), 0.76 – 0.59 (m, 4H), 0.10 – 0.06 (m, 2H).

Step 2

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-(4-methoxypiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **399-2**

Compound **394d-2** (180 mg, 355.27 μmol) and 4-methoxypiperidine (49.10 mg, 426.33 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (21.33 mg, 355.27 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (66.98 mg, 1.07 mmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 44%-74%), to obtain the title Compound **399-2** (65.83 mg, 108.66 μmol, yield: 30.59%) as yellow solid.

Single-configuration Compound 399-2:

MS m/z (ESI):606.8 [M+1]

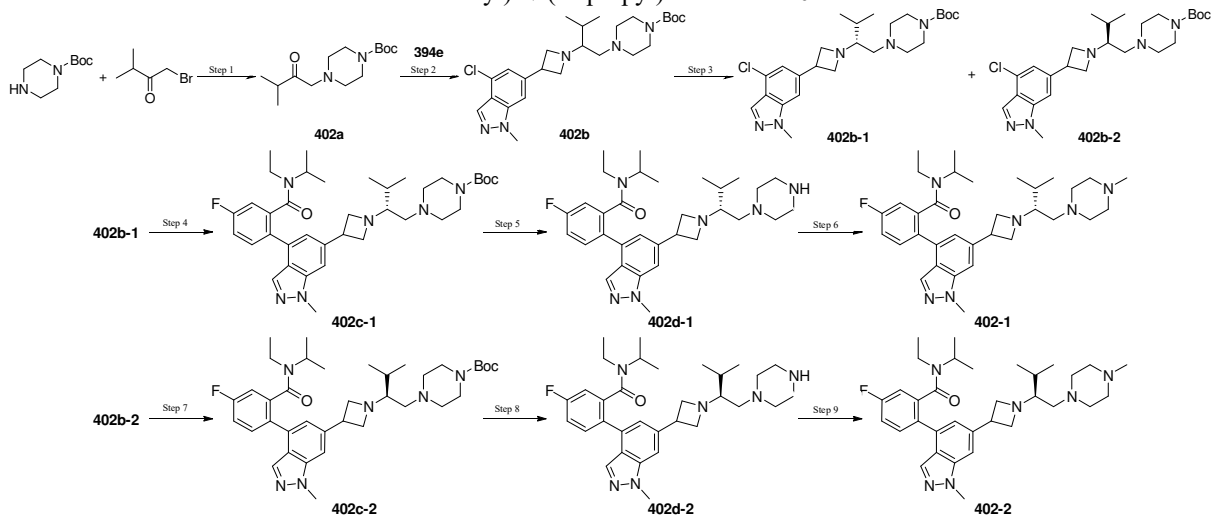
Chiral SFC: retention time: 1.145 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.75 (m, 1H), 7.63 – 7.46 (m, 2H), 7.42 – 7.22 (m, 2H), 7.14 – 6.99 (m, 1H), 4.04 (s, 3H), 3.64 (s, 3H), 3.32 – 3.06 (m, 7H), 2.87 – 2.73 (m, 1H), 2.67 – 2.56 (m, 2H), 2.23 – 2.15 (m, 2H), 2.08 – 1.90 (m, 3H), 1.84 – 1.66 (m, 3H), 1.50 – 0.78 (m, 16H), 0.76 – 0.58 (m, 4H), 0.12 – 0.03 (m, 2H).

Examples 402-1 and 402-2

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402-1**

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402-2**



Step 1

4-(3-methyl-2-oxobutyl)piperazin-1-tert-butyl carboxylate **402a**

Piperazin-1-tert-butyl carboxylate (2.2 g, 11.81 mmol) was dissolved in DMF(30 mL), followed by the addition of 1-bromo-3-methyl-but-2-one (2.05 g, 12.40 mmol) and potassium carbonate (4.90 g, 35.44 mmol) at 25°C. The reaction mixture was heated to 80°C and stirred for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, washed with water (20 mL x 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **402a** (2.29 g, 8.47 mmol, yield: 71.71%) as yellow oil.

MS m/z (ESI): 271.1 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 – 3.38 (m, 4H), 3.23 (s, 2H), 2.72 – 2.56 (m, 1H), 2.43 – 2.33 (m, 4H), 1.39 (s, 9H), 1.03 (d, J = 7.2 Hz, 6H).

Step 2

4-{2-[3-(4-chloro-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-3-methylbutyl}piperazin-1-tert-butyl carboxylate **402b**

Compound **394e** (400 mg, 1.80 mmol) and Compound **402a** (634.19 mg, 2.35 mmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (491.85 mg, 3.61 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (340.17 mg, 5.41 mmol) and stirring at 50°C for 11 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **402b** (720 mg, 1.51 mmol, yield: 83.82%) as yellow oil.
MS m/z (ESI): 476.4 [M+1]

Step 3

4-[(2*R*)-2-[3-(4-chloro-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **402b-1**

4-[(2*S*)-2-[3-(4-chloro-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **402b-2**

Compound **402b** (320 mg, 672.19 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-methanol (0.1 ammonia water); elution gradient: 15%), to obtain the title Compounds **402b-1** (135 mg, 283.58 μmol, yield: 42.19%) and **402b-2** (120 mg, 252.07 μmol, yield: 37.50%).

Single-configuration Compound 402b-1:

MS m/z (ESI): 476.4 [M+1]
Chiral HPLC analysis: retention time: 1.094 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 402b-2:

MS m/z (ESI): 476.4 [M+1]
Chiral HPLC analysis: retention time: 1.296 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 4

4-[(2*R*)-2-[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl)-3-methylbutyl)piperazin-1-tert-butyl carboxylate **402c-1**

Compound **402b-1** (130.00 mg, 273.08 μmol), Compound **4c**(228.85 mg, 409.62 μmol) and potassium phosphate (173.90 mg, 819.24 μmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). Pd(dtbpf)Cl_2 (17.80 mg, 27.31 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **402c-1** (110 mg, 169.53 μmol, yield: 62.08%) as oil.
MS m/z (ESI): 649.5

Step 5

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*R*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402d-1**

Compound **402c-1** (110 mg, 169.53 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure to obtain the crude product of title Compound **402d-1** (90 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 549.4 [M+1]

Step 6

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402-1**

The crude product of Compound **402d-1** (90 mg) and formaldehyde (24.62 mg, 246.02 μmol) were dissolved in methanol (3.0 mL), followed by the addition of triethylamine (49.79 mg, 492.04 μmol). Under the protection of

nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (30.92 mg, 492.04 μmol) was added, allowing for reacting at room temperature for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 49%-79%), to obtain the title Compound **402-1** (71.05 mg, 126.25 μmol, yield: 76.98%).

Single-configuration Compound 402-1:

MS m/z (ESI):563.4 [M+1]

Chiral SFC: retention time: 0.656 min; chromatographic column: Chiralcel OJ-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 – 7.76 (m, 1H), 7.64 – 7.55 (m, 1H), 7.54 – 7.46 (m, 1H), 7.43 – 7.25 (m, 2H), 7.18 – 7.02 (m, 1H), 4.04 (s, 3H), 3.74 – 3.60 (m, 3H), 3.43 – 3.35 (m, 1H), 3.31 – 3.09 (m, 3H), 2.89 – 2.76 (m, 1H), 2.46 – 2.14 (m, 10H), 2.10 (s, 3H), 1.83 – 1.69 (m, 1H), 1.08 – 0.77 (m, 10H), 0.67 (t, J = 6.8 Hz, 4H), 0.08 (d, J = 6.0 Hz, 2H).

Step 7

4-[(2*S*)-2-[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl)-3-methylbutyl)piperazin-1-tert-butyl carboxylate **402c-2**

Compound **402b-2** (120 mg, 252.07 μmol), Compound **4c**(228.85 mg, 409.62 μmol) and potassium phosphate (160.52 mg, 756.22 μmol) were dissolved in dioxane (5.0 mL) and water (1.0 mL). Pd(dtbpf)Cl_2 (16.43 mg, 25.21 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the crude product of title Compound **402-2** (185 mg, 285.12 μmol, yield: 113%) as oil.

MS m/z (ESI): 649.3[M+1]

Step 8

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*S*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402d-2**

Compound **402c-2** (500 mg, 1.94 mmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.40 g, 12.28 mmol, 945.67 μL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding dichloromethane (30 mL), regulated to alkaline pH with a 10 % aqueous NaOH solution (40 mL), and let stand for separation, and the aqueous phase was extracted with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **402d-2** (156 mg, 284.29 μmol, yield: 99.71%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 549.4 [M+1]

Step 9

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **402-2**

The crude product of Compound **402d-2** (156 mg, 284.29 μmol) and formaldehyde (85.36 mg, 2.84 mmol) were dissolved in methanol (5.0 mL). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (53.60 mg, 852.87 μmol) was added, allowing for reacting at room temperature for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 48%-78%), to obtain the title Compound **402-2** (62.82 mg, 111.63 μmol, yield: 39.27%) as white solid.

Single-configuration Compound 402-2:

MS m/z (ESI):563.3 [M+1]

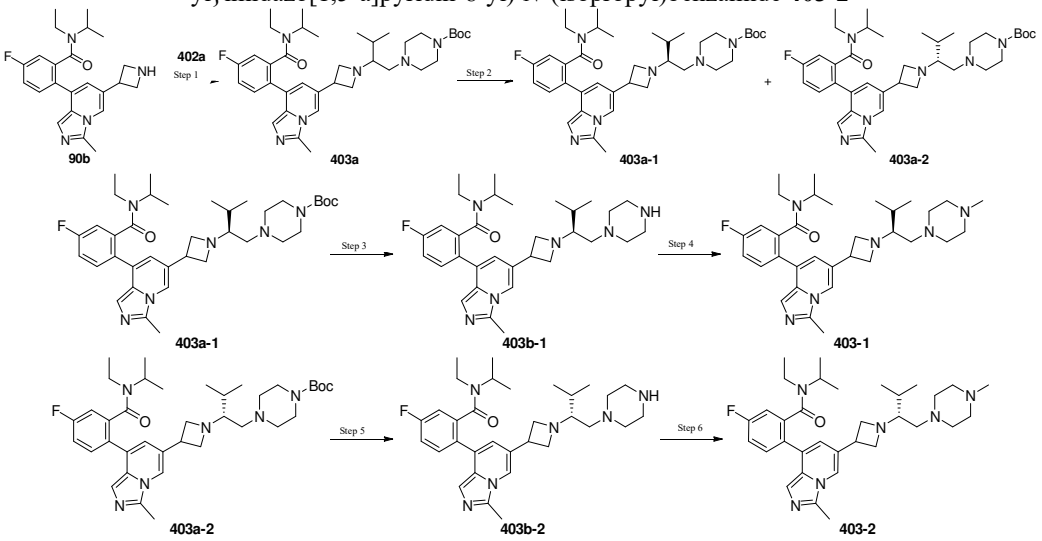
Chiral SFC: retention time: 0.891 min; chromatographic column: Chiralpak AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 1H), 7.56 – 7.45 (m, 1H), 7.23 (br s, 1H), 7.19 – 7.06 (m, 3H), 4.04 (s, 3H), 4.00 – 3.73 (m, 2H), 3.52 – 3.21 (m, 3H), 2.86 – 2.68 (m, 1H), 2.65 – 2.14 (m, 13H), 1.89 – 1.37 (m, 4H), 1.24 – 0.55 (m, 13H), -0.01 (d, J = 6.6 Hz, 2H).

Examples 403-1 and 403-2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403-1**

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403-2**



Step 1

4-{2-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl}piperazin-1-tert-butyl carboxylate **403a**

Compound **90b** (500 mg, 1.27 mmol) and Compound **402a** (411.22 mg, 1.52 mmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (345.50 mg, 2.53 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (238.95 mg, 3.80 mmol) and stirring at 50℃ for 8.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **403a** (500 mg, 770.59 μmol, yield: 60.80%) as yellow solid.

MS m/z (ESI): 649.7 [M+1]

Step 2

4-[(2S)-2-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **403a-1**

tert-butyl 4-[(2R)-2-[3-(8-{2-[ethyl(propan-2-yl)carbamoyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azetidin-1-yl]-3-methylbutyl]piperazine-1-carboxylate

4-[(2R)-2-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl]piperazin-1-tert-butyl carboxylate **403a-2**

Compound **403a** (350 mg, 926.15 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OX (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-methanol; elution gradient: 40%), to obtain the title Compounds **403a-1** (140 mg, 215.77 μmol, yield: 35.0%) and **403a-2** (140 mg, 215.77 μmol, yield: 35.0%).

Single-configuration Compound 403a-1:

MS m/z (ESI): 649.5 [M+1]

Chiral HPLC analysis: retention time: 2.078 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 403a-2:

MS m/z (ESI): 649.6 [M+1]

Chiral HPLC analysis: retention time: 2.267 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*S*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403b-1**

Compound **403a-1** (100.00 mg, 154.12 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure to obtain the crude product of title Compound **403b-1** (80 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 549.4 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*S*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403-1**

The crude product of Compound **403b-1** (80 mg) and formaldehyde (54.91 mg, 603.54 μmol) were dissolved in methanol (3.0 mL), followed by the addition of triethylamine (24.43 mg, 241.41 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (22.76 mg, 362.12 μmol) was added, allowing for reacting at room temperature for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 38%-68%), to obtain the title Compound **403-1** (44.46 mg, 79.00 μmol, yield: 65.45%).

Single-configuration Compound 403-1:

MS m/z (ESI):563.6 [M+1]

Chiral SFC: retention time: 1.031 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.84 (m, 1H), 7.75 – 7.58 (m, 1H), 7.44 – 7.16 (m, 2H), 7.08 – 6.97 (m, 1H), 6.92 – 6.75 (m, 1H), 3.61 – 3.40 (m, 4H), 3.28 – 3.08 (m, 3H), 2.99 – 2.84 (m, 1H), 2.58 (s, 3H), 2.54 (s, 1H), 2.43 – 2.06 (m, 13H), 1.79 – 1.66 (m, 1H), 1.11 – 0.69 (m, 13H), 0.26 (d, J = 6.8 Hz, 2H).

Step 5

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*R*)-3-methyl-1-(piperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403b-2**

Compound **402a-2** (120.00 mg, 184.94 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25℃ to allow for reacting for 0.25 hours. The reaction mixture was concentrated under a reduced pressure to obtain the crude product of title Compound **403b-2** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 549.4 [M+1]

Step 6

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(2*R*)-3-methyl-1-(4-methylpiperazin-1-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **403-2**

The crude product of Compound **403b-2** (100 mg) and formaldehyde (93.43 mg, 905.31 μmol) were dissolved in methanol (2.0 mL), followed by the addition of triethylamine (36.64 mg, 362.12 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 0.5 hour. Sodium cyanoborohydride (34.13 mg, 543.18 μmol) was added, allowing for reacting at room temperature for 2.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 38%-68%), to obtain the title Compound **403-2** (26.96 mg, 47.91 μmol, yield: 26.46%) as white solid.

Single-configuration Compound 403-2:

MS m/z (ESI):563.8 [M+1]

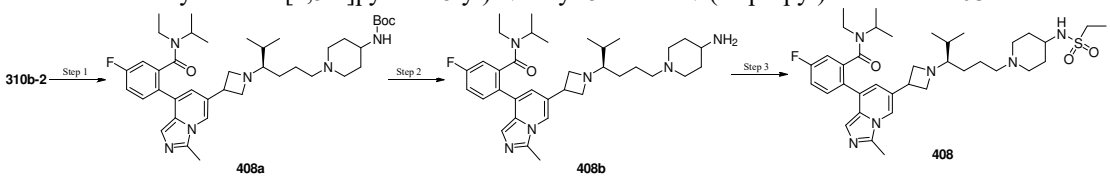
Chiral SFC: retention time: 1.523 min; chromatographic column: Chiralcel OX-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.82 (m, 1H), 7.76 – 7.61 (m, 1H), 7.46 – 7.27 (m, 2H), 7.09 – 6.97 (m, 1H), 6.93 – 6.75 (m, 1H), 4.43 – 3.33 (m, 5H), 3.31 – 3.26 (m, 1H), 3.22 – 2.72 (m, 3H), 2.58 (s, 3H), 2.43 – 2.05 (m, 13H), 1.80 – 1.67 (m, 1H), 1.11 – 0.70 (m, 13H), 0.31 – 0.23 (m, 2H).

Example 408

2-(6-{1-[(3*R*)-6-(4-ethanesulfonamidopiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-

methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **408**



Step 1

N-{1-(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl}piperidin-4-yl}tert-butyl carbamate **408a**

Compound **310b-2** (180 mg, 355.27 μmol) and *N*-(piperidin-4-yl)tert-butyl carbamate (142.31 mg, 710.55 μmol) were dissolved in methanol (4.0 mL), followed by the addition of acetic acid (21.33 mg, 355.27 μmol), and under the protection of nitrogen, the mixture was stirred at 50°C for 0.5 hours. Sodium cyanoborohydride (66.98 mg, 1.07 mmol) was added, and the mixture was stirred at 50℃ to allow for reacting for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **408a** (180 mg, 260.52 μmol, yield: 73.33%) as yellow solid.

MS m/z (ESI):691.5 [M+1]

Step 2

2-(6-{1-[(3*R*)-6-(4-aminopiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **408b**

Compound **408a** (180 mg, 260.52 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (10 mL), regulated to PH = 10 by adding a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **408b** (150 mg, 253.89 μmol, yield: 97.45%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI):591.5 [M+1]

Step 3

2-(6-{1-[(3*R*)-6-(4-ethanesulfonamidopiperidin-1-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **408**

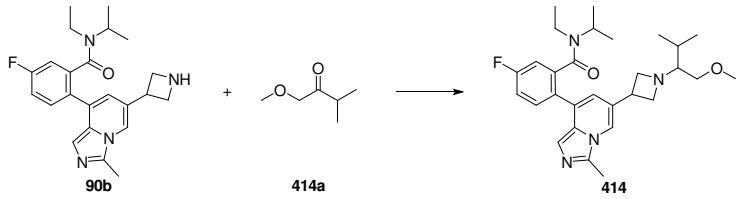
408b (150.00 mg, 253.89 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (77.07 mg, 761.66 μmol), and the mixture was cooled in an ice bath while ethanesulfonyl chloride (39.17 mg, 304.66 μmol) was added, allowing for a reaction at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:36%-66%). The title Compound **408** (29.44 mg, 43.11 μmol, yield: 16.98%) was obtained as white solid.

MS m/z (ESI): 683.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.89 (m, 1H), 7.81 – 7.56 (m, 1H), 7.48 – 7.21 (m, 2H), 7.18 – 6.91 (m, 2H), 6.87 – 6.58 (m, 1H), 3.60 – 3.48 (m, 3H), 3.04 – 2.90 (m, 4H), 2.77 – 2.67 (m, 2H), 2.61 – 2.56 (m, 3H), 2.55 – 2.53 (m, 4H), 2.25 – 2.13 (m, 2H), 2.05 – 1.98 (m, 1H), 1.93 – 1.80 (m, 2H), 1.79 – 1.66 (m, 3H), 1.48 – 1.35 (m, 4H), 1.27 – 1.06 (m, 6H), 0.93 – 0.71 (m, 12H), 0.30 – 0.24 (m, 2H).

Example 414

N-ethyl-5-fluoro-2-{6-[1-(1-methoxy-3-methylbutan-2-yl)azacyclobutan-3-yl]-3-methylimidazo[1,5-a]pyridin-8-yl}-*N*-(isopropyl)benzamide **414**



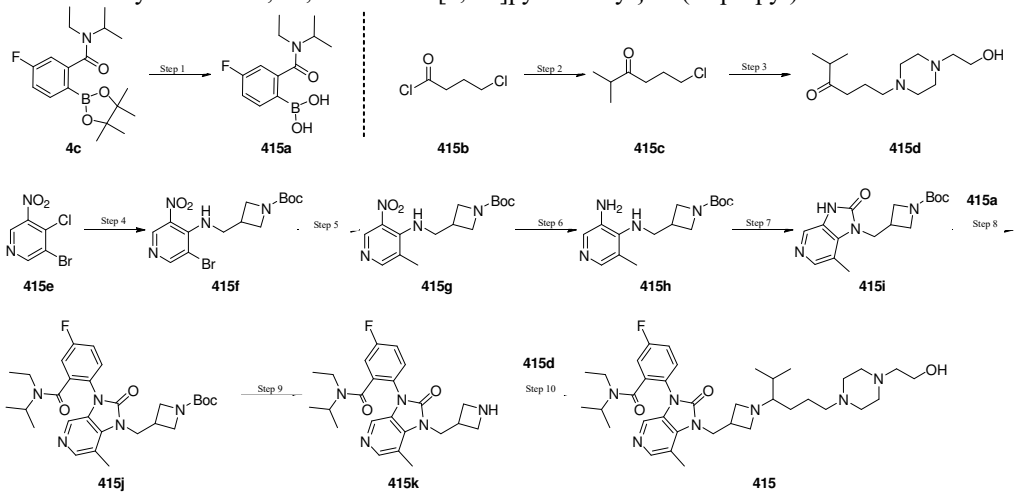
Compound **90b** (110 mg, 278.85 μmol) and 1-methoxy-3-methylbutan-2-one **414a** (64.78 mg, 557.69 μmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (76.01 mg, 557.69 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (43.81 mg, 697.11 μmol) and stirring at 50°C for 8.0 hours. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 38%-68%). The title Compound **414** (25 mg, 50.54 μmol, yield: 18.13%) was obtained.

MS m/z (ESI):495.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.88 (m, 1H), 7.73 – 7.62 (m, 1H), 7.44 – 7.26 (m, 2H), 7.07 – 7.00 (m, 1H), 6.84 – 6.72 (m, 1H), 3.62 – 3.40 (m, 4H), 3.32 – 3.07 (m, 8H), 2.97 – 2.87 (m, 1H), 2.59 (s, 3H), 2.30 – 2.24 (m, 1H), 1.79 – 1.66 (m, 1H), 1.10 – 0.72 (m, 13H), 0.31 – 0.24 (m, 2H).

Example 415

N-ethyl-5-fluoro-2-{1-[(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)methyl]-7-methyl-2-oxo-1*H*,2*H*,3*H*-imidazo[4,5-c]pyridin-3-yl} *N*-(isopropyl)benzamide **415**



Step 1

{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}boric acid **415a**

Compound **4c** (1 g, 1.49 mmol) was dissolved in DCM (5.0 mL), followed by the slow addition of trifluoroacetic acid (510.20 mg, 4.47 mmol) and methylboric acid (267.85 mg, 4.47 mmol), and the mixture was stirred at 25°C to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the reverse phase column chromatography (column: Spherical C18, 20-35 μm, 100 A, 120 g; mobile phase: acetonitrile, water, elution gradient: 50%-60%), to obtain the title Compound **415a** (320 mg, 1.26 mmol, yield: 84.77%).

MS m/z (ESI): 236.2 $[M-F+H]^+$

Step 2

6-chloro-2-methylhexan-3-one **415c**

4-Chlorobutyryl chloride **415b** (30 g, 212.77 mmol) was dissolved in anhydrous tetrahydrofuran (500 mL), followed by the addition of the tetrahydrofuran solution (100 mL) of iron (III) acetylacetonate (1.80 g, 5.11 mmol), and the mixture was stirred for 10 min. The mixture was cooled to 0°C, followed by the slow dropwise addition of isopropylmagnesium chloride (2 M, 107 mL). The reaction mixture was stirred at 0°C for 0.5 hours. A saturated aqueous ammonium chloride solution (100 mL) was then slowly added, and the mixture was fully stirred. The mixture was concentrated under a reduced pressure to remove tetrahydrofuran, and the remaining aqueous phase was extracted with ethyl acetate (100 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title

Compound **415c** (21.4 g, 143.98 mmol, yield: 67.67%) as colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 – 3.61 (m, 2 H), 2.53 – 2.71 (m, 3 H), 2.01 – 2.09 (m, 2 H), 1.10 (d, J=7.20 Hz, 6 H).

Step 3

6-[4-(2-hydroxyethyl)piperazine -1-yl]-2-methylhexan-3-one **415d**

Compound **415c** (11.4 g, 69.03 mmol) was dissolved in acetonitrile (120 mL), followed by the addition of 2-(piperazine -1-yl)ethanol (8.99 g, 69.03 mmol) and DIPEA(26.68 g, 206.44 mmol). Under a nitrogen atmosphere, the mixture was stirred at 80°C to allow for reacting for 16.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The residues was added to a saturated aqueous potassium carbonate solution (200 mL), and the resulting mixture was extracted with dichloromethane (100 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **415d** (17.4 g, 71.80 mmol, yield: 104%) as brown oil.
MS m/z (ESI): 243.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 (br s, 1 H), 3.46 (br s, 2 H), 2.57 – 2.65 (m, 1 H), 2.45 (br t, J=6.80 Hz, 2 H), 2.22 – 2.40 (m, 10 H), 2.18 (br t, J=7.20 Hz, 2 H), 1.59 (br t, J=6.80 Hz, 2 H), 0.99 (d, J=6.80 Hz, 6 H).

Step 4

3-{[(3-bromo-5-nitropyridin-4-yl)amino]methyl}azacyclobutan-1-tert-butyl carboxylate **415f**

3-Bromo-4-chloro-5-nitropyridine **415e** (7.0 g, 29.48 mmol) and 3-(aminomethyl)azacyclobutan-1-tert-butyl carboxylate (4.39 g, 23.59 mmol) were dissolved in tetrahydrofuran (50 mL), followed by the addition of triethylamine (5.97 g, 58.96 mmol). The mixture was stirred at room temperature to allow for reacting for 12 hours. The reaction mixture was diluted with ethyl acetate (150.0 mL), and washed with a saturated aqueous ammonium chloride solution (150 mL x 3). The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **415f** (8.7 g, 22.47 mmol, yield: 76.21%) as yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.52 (s, 1H), 4.10 (t, J = 8.5 Hz, 2H), 3.84 (dd, J = 5.4, 7.1 Hz, 2H), 3.68 (dd, J = 4.9, 8.9 Hz, 2H), 2.84 (tddd, J = 2.5, 5.1, 7.6, 12.7 Hz, 1H), 1.45 (s, 9H).

Step 5

3-{[(3-methyl-5-nitropyridin-4-yl)amino]methyl}azacyclobutan-1-tert-butyl carboxylate **415g**

Compound **415f** (4 g, 10.33 mmol), methylboric acid (1.24 g, 20.66 mmol) and potassium phosphate (6.58 g, 30.99 mmol) were dissolved in dioxane (40 mL). CataCXium A Pd-G3 (752.29 mg, 1.03 mmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding ethyl acetate (150 mL) and washing with water (150 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **415g** (2.2 g, 6.82 mmol, yield: 66.07%) as yellow solid.
MS m/z (ESI): 323.1 [M+1]

Step 6

3-{[(3-amino-5-methylpyridin-4-yl)amino]methyl}azacyclobutan-1-tert-butyl carboxylate **415h**

Compound **415g** (1.9 g, 5.89 mmol) was dissolved in water (4.0 mL) and ethanol (20 mL). Ammonium chloride (1.58 g, 29.47 mmol) was added, and iron powder (3.29 g, 58.94 mmol) was added while stirring was performed. The reaction mixture was heated to 80°C and stirred for 1.0 hour. The mixture was diluted with ethyl acetate (250 mL), and washed with water (250 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%), to obtain the title Compound **415h** (550 mg, 1.71 mmol, yield: 28.95%) as white solid.
MS m/z (ESI): 293.2[M+1]

Step 7

3-({7-methyl-2-oxo-1*H*,2*H*,3*H*-imidazo[4,5-c]pyridin-1-yl}methyl)azacyclobutan-1-tert-butyl carboxylate **415i**

Compound **415h** (500 mg, 1.71 mmol) was dissolved in acetonitrile (10 mL), followed by the addition of 1,1-carbonyldiimidazole (831.89 mg, 2.57 mmol, 50%purity) and DIPEA(265.23 mg, 2.05 mmol). The mixture was stirred at 25°C to allow for reacting for 12.0 hours. The reaction mixture was diluted with ethyl acetate (50 mL), and extracted with water (50 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **415i** (470 mg, 1.48 mmol, yield: 86.33%) as white solid.

MS m/z (ESI): 319.1[M+1]

Step 8

tert-butyl3-[(3-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}7-methyl-2-oxo-1*H*,2*H*,3*H*-imidazol[4,5-c]pyridin-1-yl)methyl]azacyclobuten-1-tert-butyl carboxylate **415j**

Compound **415i** (100 mg, 314.10 μmol) was dissolved in dichloromethane (4.0 mL). Compound **415a** (1.24 g, 20.66 mmol), copper acetate (28.53 mg, 157.05 μmol), 2,2'-bipyridine (24.53 mg, 157.05 μmol) and cesium carbonate (204.68 mg, 628.20 μmol) were added. 4Å molecular sieve (100 mg) was added, and the mixture was stirred at 25°C to allow for reacting for 3.0 hours under an oxygen atmosphere. Ethyl acetate (30 mL) was added to the reaction mixture, which was then washed with water (30 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **415j** (80 mg, 152.20 μmol, yield: 48.46%) as oil.

MS m/z (ESI): 526.3[M+1]

Step 9

2-{1-[(azacyclobutan-3-yl)methyl]-7-methyl-2-oxo-1*H*,2*H*,3*H*-imidazo[4,5-c]pyridin-3-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **415k**

Compound **415j** (70 mg, 133.18 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (2.07 g, 18.17 mmol, 1.40 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, then dissolved by adding (3.0 mL), followed by adding a 10% aqueous sodium hydroxide solution (10 mL) and extracting with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **415k** (56 mg, 131.61 μmol, yield: 98.82%) as brown oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI):426.4 [M+1]

Step 10

N-ethyl-5-fluoro-2-{1-[(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)methyl]-7-methyl-2-oxo-1*H*,2*H*,3*H*-imidazo[4,5-c]pyridin-3-yl} *N*-(isopropyl)benzamide **415**

The crude product of Compound **415k** (56 mg, 131.61 μmol) and Compound **415d** (31.90 mg, 131.61 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (7.90 mg, 131.61 μmol), and the mixture was stirred at 50°C for 0.5 hours under the protection of nitrogen.Sodium cyanoborohydride (24.81 mg, 394.83 μmol) was added, allowing for reacting at 50°C for 12.0 hours under the protection of nitrogen. Ethyl acetate (20 mL) was added to the reaction mixture, which was then washed with water (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 22%-52%), to obtain the title Compound **415** (23.76 mg, 36.45 μmol, yield: 27.7%).

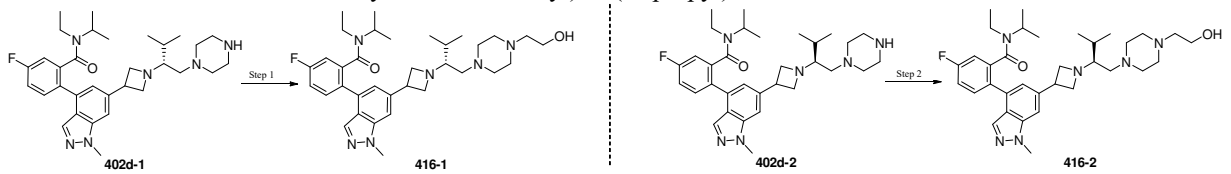
MS m/z (ESI):652.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.81 – 7.76 (m, 1H), 7.60 (dd, J = 4.8, 9.2 Hz, 1H), 7.52 – 7.41 (m, 2H), 4.40 – 4.15 (m, 3H), 3.78 – 3.68 (m, 1H), 3.46 (t, J = 6.4 Hz, 3H), 3.17 – 3.11 (m, 2H), 3.03 – 2.89 (m, 3H), 2.69 – 2.65 (m, 1H), 2.58 – 2.54 (m, 4H), 2.41 – 2.24 (m, 9H), 2.20 – 2.14 (m, 2H), 1.94 – 1.88 (m, 1H), 1.70 – 1.58 (m, 1H), 1.43 – 1.31 (m, 2H), 1.21 – 0.96 (m, 8H), 0.87 – 0.74 (m, 7H), 0.72 – 0.63 (m, 2H).

Examples 416-1 and 416-2

N-ethyl-5-fluoro-2-(6-{1-[(2*R*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **416-1**

N-ethyl-5-fluoro-2-(6-{1-[(2*S*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **416-2**



402d-1 416-1 402d-2 416-2

Step 1

N-ethyl-5-fluoro-2-(6-{1-[(2*R*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **416-1**

Compound **402d-1** (150 mg, 273.36 μmol), 2-bromoethanol (40.99 mg, 328.03 μmol), potassium carbonate (113.34 mg, 820.07 μmol) and sodium iodide (4.10 mg, 27.34 μmol) were dissolved in acetonitrile (3.0 mL). Under the

protection of nitrogen, the mixture was stirred at 85°C for 2.0 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 37%-67%), to obtain the title Compound **416-1** (29.73 mg, 50.15 μmol, yield: 18.35%) as white solid.

Single-configuration Compound 416-1:

MS m/z (ESI):593.9 [M+1]

Chiral SFC: retention time: 1.177 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.75 (m, 1H), 7.63 – 7.47 (m, 2H), 7.42 – 7.24 (m, 2H), 7.18 – 7.03 (m, 1H), 4.35 – 4.28 (m, 1H), 4.04 (s, 3H), 3.73 – 3.61 (m, 3H), 3.49 – 3.34 (m, 3H), 3.29 – 3.10 (m, 3H), 2.91 – 2.54 (m, 2H), 2.45 – 2.24 (m, 10H), 2.18 – 2.12 (m, 2H), 1.82 – 1.67 (m, 1H), 1.02 – 0.65 (m, 13H), 0.08 (d, J = 5.2 Hz, 2H).

Step 2

N-ethyl-5-fluoro-2-(6-{1-[(2*S*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **416-2**

Compound **402d-2** (100 mg, 182.24 μmol), 2-bromoethanol (27.33 mg, 218.68 μmol) and potassium carbonate (113.34 mg, 820.07 μmol) were dissolved in acetonitrile (2.0 mL). Under the protection of nitrogen, the mixture was stirred at 85°C for 2.0 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 37%-67%), to obtain the title Compound **416-2** (20.98 mg, 35.39 μmol, yield: 19.42%) as yellow solid.

Single-configuration Compound 416-2:

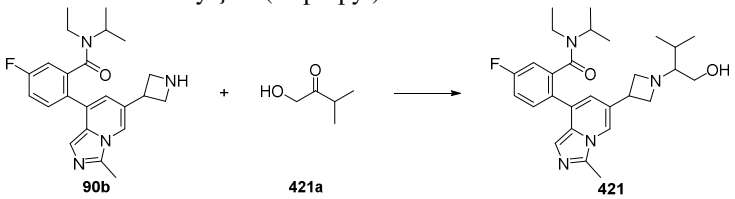
MS m/z (ESI):593.5 [M+1]

Chiral SFC: retention time: 1.157 min; chromatographic column: Chiralpak OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.68 (m, 1H), 7.65 – 7.45 (m, 2H), 7.44 – 7.23 (m, 2H), 7.18 – 7.04 (m, 1H), 4.35 – 4.21 (m, 1H), 4.12 – 3.93 (m, 3H), 3.72 – 3.59 (m, 3H), 3.48 – 3.33 (m, 3H), 3.31 – 3.07 (m, 4H), 2.89 – 2.59 (m, 2H), 2.45 – 2.20 (m, 10H), 2.18 – 2.12 (m, 2H), 1.83 – 1.71 (m, 1H), 1.26 – 0.96 (m, 1H), 0.92 – 0.80 (m, 8H), 0.71 – 0.64 (m, 3H), 0.11 – 0.04 (m, 2H).

Example 421

N-ethyl-5-fluoro-2-{6-[1-(1-hydroxyl-3-methylbutan-2-yl)azacyclobutan-3-yl]-3-methylimidazo[1,5-a]pyridin-8-yl}-*N*-(isopropyl)benzamide **421**



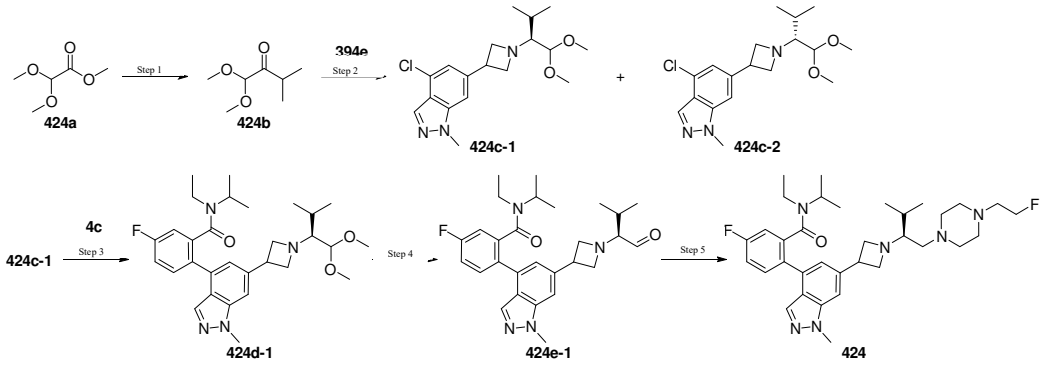
Compound **90b** (100 mg, 253.50 μmol) and 1-hydroxyl-3-methylbutan-2-one **421a** (51.78 mg, 506.99 μmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (69.10 mg, 506.99 μmol), and the mixture was stirred at 55°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (47.79 mg, 760.49 μmol) and stirring at 55°C for 11 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%). The title Compound **421** (1.16 mg, 2.41 μmol) was obtained.

MS m/z (ESI):481.2 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.93 – 7.81 (m, 1H), 7.75 – 7.64 (m, 1H), 7.37 – 7.26 (m, 1H), 7.24 – 7.17 (m, 1H), 7.12 (s, 1H), 6.94 – 6.84 (m, 1H), 3.89 – 3.33 (m, 9H), 3.13 – 2.96 (m, 1H), 2.65 (s, 3H), 2.39 – 2.26 (m, 1H), 1.97 – 1.77 (m, 1H), 1.14 – 0.78 (m, 13H), 0.33 (s, 2H).

Example 424

N-ethyl-5-fluoro-2-(6-{1-[(2*S*)-1-[4-(2-fluoroethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **424**



Step 1

1,1-dimethoxy-3-methylbutan-2-one **424b**

Under the protection of nitrogen, 2,2-dimethoxymethyl acetate (2 g, 14.91 mmol) and *N*-methoxymethylamine (1.82 g, 18.64 mmol) were dissolved in tetrahydrofuran (20 mL), and cooled to -40°C under the protection of nitrogen, followed by the slow dropwise addition of isopropylmagnesium bromide solution (3.0 M, 12.43 mL). After the completion of dropwise addition, the mixture was further stirred at -40°C for 2.0 hours. The reaction mixture was quenched by adding water (1.0 mL) and a saturated aqueous ammonium chloride solution (1.0 mL), then diluted by adding water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **424b** (800 mg, 5.47 mmol, yield: 36.70%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (s, 1H), 3.33 (s, 6H), 2.99 – 2.89 (m, 1H), 1.03 (d, J = 6.9 Hz, 6H).

Step 2

4-chloro-6-{1-[(2*S*)-1,1-dimethoxy-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **424c-1**

4-chloro-6-{1-[(2*R*)-1,1-dimethoxy-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazole **424c-2**

Compound **394e** (344 mg, 1.55 mmol) and Compound **424b**(415.87 mg, 1.71 mmol) were dissolved in methanol (20 mL), and stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (292.54 mg, 4.66 mmol) and stirring at 50°C for 11 hour. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was separated and purified by the chiral preparative HPLC (preparative column: Phenomenex-Cellulose-2 (250 mm * 30 mm,5 um), mobile phase: carbon dioxide-methanol (0.1 ammonia water); elution gradient: 17%), to obtain the title Compounds **424c-1** (208 mg, 591.13 μmol, yield: 38.09%) and **424c-2** (247 mg, 701.96 μmol, yield: 45.24%).

Single-configuration Compound 424c-1:

MS m/z (ESI): 352.0 [M+1]

Chiral HPLC analysis: retention time: 1.587 min; chromatographic column: Cellulose-2 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 424c-2:

MS m/z (ESI): 352.0 [M+1]

Chiral HPLC analysis: retention time: 1.474 min; chromatographic column: Cellulose-2 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

2-(6-{1-[(2*S*)-1,1-dimethoxy-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **424d-1**

Compound **424c-1** (208 mg, 591.13 μmol), Compound **4c**(495.39 mg, 886.69 μmol) and potassium phosphate (376.43 mg, 1.77 mmol) were dissolved in dioxane (10 mL) and water (2.0 mL). $Pd(dtbpf)Cl_2$ (38.53 mg, 59.11 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **424d-1** (310 mg, 590.85 μmol, yield: 99.95%) as oil.

MS m/z (ESI): 525.3

Step 4

N-ethyl-5-fluoro-2-(1-methyl-6-{1-[(2*S*)-3-methyl-1-oxabutan-2-yl]azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **424e-1**

Compound **424d-1** (330 mg, 628.97 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (8.88 g, 77.88 mmol, 6 mL). The mixture was stirred at 30℃ to allow for reacting for 24 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 10 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **424e-1** (311 mg, 626.24 μmol, yield: 99.57%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 497.4 [M+18+1]

Step 5

N-ethyl-5-fluoro-2-(6-{1-[(2*S*)-1-[4-(2-fluoroethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **424**

Compound **424e-1** (240 mg, 483.28μmol) and 1-(2-fluoroethyl)piperazine (99.42 mg, 752.20 μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (30.12 mg, 501.46 μmol). Under the protection of nitrogen, the mixture was stirred at 35℃ for 1.0 hours. Sodium cyanoborohydride (94.54 mg, 1.50 mmol) was added, allowing for reacting at room temperature for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the test reaction mixture, which was then extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 40%-70%), to obtain the title Compound **424** (3.1 mg, 5.21 μmol, yield: 2.08%) as yellow solid.

Single-configuration Compound 424

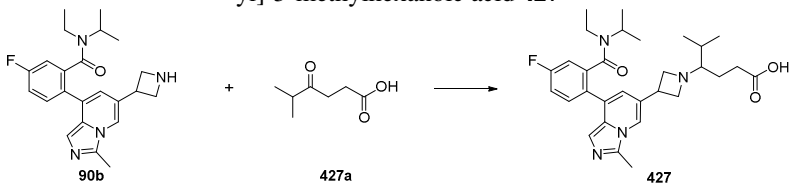
MS m/z (ESI):595.4 [M+1]

Chiral SFC: retention time: 1.032 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.65 – 7.47 (m, 2H), 7.44 – 7.25 (m, 2H), 7.18 – 7.04 (m, 1H), 4.59 – 4.50 (m, 1H), 4.46 – 4.39 (m, 1H), 4.04 (s, 3H), 3.74 – 3.59 (m, 3H), 3.27 – 3.15 (m, 2H), 2.89 – 2.54 (m, 3H), 2.44 – 2.15 (m, 9H), 1.83 – 1.70 (m, 1H), 1.33 – 0.94 (m, 4H), 0.94 – 0.78 (m, 9H), 0.74 – 0.57 (m, 4H), 0.11 – 0.05 (m, 2H).

Example 427

4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexanoic acid **427**



90b 427a 427

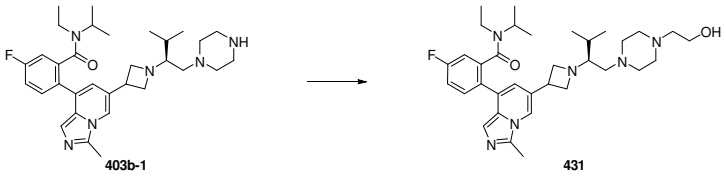
Compound **90b** (119 mg, 301.66 μmol) and 5-methyl-4-oxohexanoic acid **427a** (52.19 mg, 361.99 μmol) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$ (82.23 mg, 603.32 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (56.87 mg, 904.98 μmol) and stirring at 50℃ for 11 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% hydrochloric acid), elution gradient:2%-32%)the residues were purified . The title Compound **427** (14.74 mg, 28.20 μmol, yield: 9.35%) was obtained as white solid.

MS m/z (ESI):523.3 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.41 (m, 1H), 7.95 – 7.81 (m, 1H), 7.77 – 7.66 (m, 1H), 7.47 – 7.15 (m, 3H), 4.76 – 4.11 (m, 6H), 3.72 – 3.35 (m, 3H), 3.13 – 2.96 (m, 4H), 2.55 (br t, J = 7.2 Hz, 2H), 2.27 – 2.12 (m, 1H), 2.07 – 1.76 (m, 2H), 1.15 – 0.86 (m, 13H), 0.68 – 0.50 (m, 2H).

Example 431

N-ethyl-5-fluoro-2-(6-{1-[(2*S*)-1-[4-(2-hydroxylethyl)piperazin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-3methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **431**



403b-1 431

Compound **403b-1** (101 mg, 184.06 μmol) was dissolved in acetonitrile (5.0 mL), followed by the addition of potassium carbonate (97.90 mg, 552.18 μmol) and 2-bromoethanol (27.60 mg, 220.87 μmol). Under the protection of nitrogen, the mixture was stirred at 80°C to allow for reacting for 12 hours. Water (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **431** (34.21 mg, 57.71 μmol, yield: 31.35%) as yellow solid.

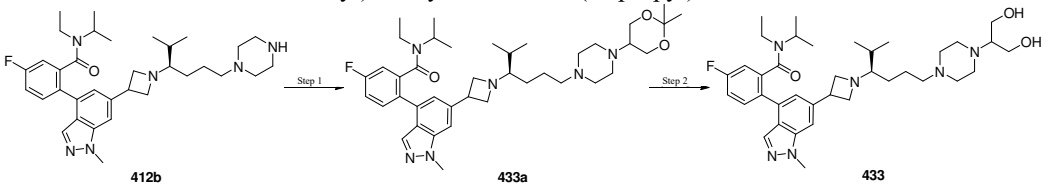
MS m/z (ESI):593.3 [M+1]

Chiral SFC: retention time: 1.129 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 4.0 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.43 – 7.27 (m, 2H), 7.07 – 7.00 (m, 1H), 6.91 – 6.74 (m, 1H), 4.39 – 4.27 (m, 1H), 3.64 – 3.39 (m, 6H), 3.32 – 2.89 (m, 4H), 2.59 (s, 3H), 2.47 – 2.09 (m, 13H), 1.80 – 1.67 (m, 1H), 1.07 – 0.72 (m, 13H), 0.27 (br d, J = 6.4 Hz, 2H).

Example 433

2-(6-{1-[(3*R*)-6-[4-(1,3-dihydroxylpropan-2-yl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **433**



412b 433a 433

Step 1

2-(6-{1-[(3*R*)-6-[4-(2,2-dimethyl-1,3-dioxacyclohexan-5-yl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **433a**

Compound **412b** (130 mg, 225.39 μmol) and 2,2-dimethyl-1,3-dioxacyclohexan-5-one (44.00 mg, 338.08 μmol) were dissolved in methanol (3.0 mL). $ZnCl_2$ (61.44 mg, 450.77 μmol) was added, and the mixture was stirred at 50°C for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (42.49 mg, 676.16 μmol) was added, allowing for reacting at 50°C for 8.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **433a** (150 mg, 217.10 μmol, yield: 96.34%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI):691.6[M+1]

Step 2

2-(6-{1-[(3*R*)-6-[4-(1,3-dihydroxylpropan-2-yl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-1-methyl-1*H*-indazol-4-yl)*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **433**

Compound **433a** (150 mg, 217.10 μmol) was dissolved in tetrahydrofuran (1.0 mL), followed by the addition of HCl (1 M, 1 mL), and the mixture was stirred at 25°C for 1.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-63%), to obtain the title Compound **433** (23.64 mg, 36.32 μmol, yield: 16.73%) as yellow solid.

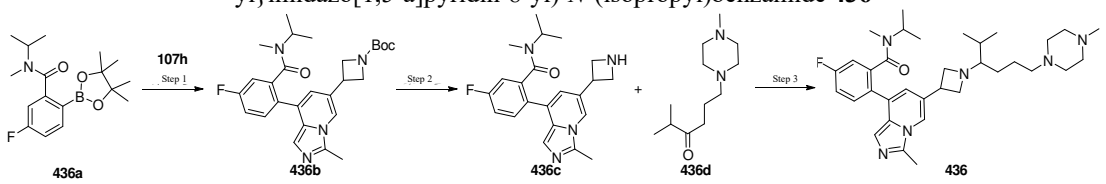
MS m/z (ESI):651.4 [M+1]

Chiral SFC: retention time: 1.305 min; chromatographic column: Chiralpak OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.78 (m, 1H), 7.63 – 7.50 (m, 2H), 7.42 – 7.35 (m, 1H), 7.33 – 7.26 (m, 1H), 7.14 – 7.01 (m, 1H), 4.22 – 4.16 (m, 2H), 4.07 – 4.02 (m, 3H), 3.70 – 3.59 (m, 3H), 3.50 – 3.36 (m, 5H), 3.31 – 3.23 (m, 1H), 3.20 – 3.06 (m, 2H), 2.87 – 2.78 (m, 1H), 2.62 – 2.55 (m, 4H), 2.44 – 2.38 (m, 1H), 2.33 – 2.25 (m, 3H), 2.22 – 2.17 (m, 2H), 2.06 – 2.00 (m, 1H), 1.78 – 1.68 (m, 1H), 1.51 – 1.39 (m, 2H), 1.31 – 1.20 (m, 2H), 1.04 – 0.63 (m, 14H), 0.10 – 0.06 (m, 2H).

Example 436

5-fluoro-*N*-methyl-2-(3-methyl-6-{1-[2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **436**



Step 1

3-(8-{4-fluoro-2-[methyl(isopropyl)aminoformyl]phenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **436b**

Compound **107h** (1.0 g, 3.11 mmol), *N*-methyl-5-fluoro-*N*-isopropyl-2-(tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **436a**(synthesized with reference to the synthesis method of Compound **4c**, 2.50 g, 4.66 mmol) and potassium phosphate (1.66 g, 7.82 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). $Pd(dtbpf)Cl_2$ (202.53 mg, 310.75 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **436b** (650 mg, 1.35 mmol, yield: 43.53%) as brown solid.

MS m/z (ESI): 481.3 [M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **436c**

Compound **436b** (150 mg, 312.13 μmol) was dissolved in methane dioxide (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding 20 mL of dichloromethane, regulated to PH = 10 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **436c** (110 mg, 289.13 μmol, 92.63%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 381.0 [M+1]

Step 3

5-fluoro-*N*-methyl-2-(3-methyl-6-{1-[2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **436**

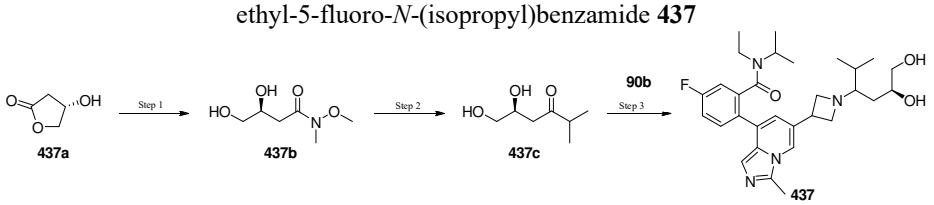
Compound **436c** (120 mg, 315.41 μmol) and 2-methyl-6-(4-methylpiperazin-1-yl)hexan-3-one **436d** (100 mg, 470.96 μmol) were dissolved in methanol (3.0 mL). $ZnCl_2$ (85.98 mg, 630.82 μmol)was added, and the mixture was stirred at 50°C for 0.5 hours. Sodium cyanoborohydride (59.46 mg, 946.23 μmol) was added, and the mixture was stirred at 50°C for 11.0 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was then extracted with dichloromethane (15 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-60%), to obtain the title Compound **436** (47.6 mg, 82.53 μmol, yield: 26.16 %) as yellow solid.

MS m/z (ESI): 577.4[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.78 – 7.66 (m, 1H), 7.44 – 7.26 (m, 2H), 7.11 – 7.01 (m, 1H), 6.89 – 6.69 (m, 1H), 4.61 – 3.44 (m, 4H), 3.20 – 2.97 (m, 2H), 2.69 – 2.56 (m, 5H), 2.38 – 1.98 (m, 15H), 1.79 – 1.65 (m, 1H), 1.52 – 1.37 (m, 2H), 1.30 – 1.14 (m, 2H), 1.06 – 0.58 (m, 11H), 0.27 – 0.22 (m, 1H).

Example 437

2-(6-{1-[(5*S*)-5,6-dihydroxyl-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **437**



Step 1

(3*S*)-3,4-dihydroxyl-*N*-methoxy-*N*-methylbutyramide **437b**

N-methoxymethylamine (8.60 g, 88.16 mmol, hydrochloride) was dissolved in dichloromethane (30 mL), and cooled to 0°C under the protection of nitrogen, followed by the slow dropwise addition of $AlMe_3$ (2.0 M, 44.08 mL). After the completion of dropwise addition, the mixture was further stirred at 0°C for 0.5 hours. Under the protection of nitrogen, the mixture was cooled to -10°C, followed by the slow dropwise addition of the solution of (4*S*)-4-hydroxyltetrahydrofuran-2-one **437a** (3 g, 29.39 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 3.0 hours. The reaction mixture was quenched by adding sodium sulfate decahydrate while being cooled in an ice-water bath, and stirred for 1.0 hour. The mixture was filtered, and the filtrate was dried over anhydrous sodium sulfate and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **437b** (2.2 g, 13.48 mmol, yield: 45.88%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.66 – 4.54 (m, 2H), 3.91 – 3.83 (m, 1H), 3.65 (s, 3H), 3.31 – 3.17 (m, 2H), 3.08 (s, 3H), 2.48 – 2.39 (m, 2H).

Step 2

(5*S*)-5,6-dihydroxyl-2-methylhexan-3-one **437c**

Under the protection of nitrogen, an isopropyllithium solution (1.0 M, 9.19 mL) was added to a reaction flask, and cooled to -78°C under the protection of nitrogen, followed by the slow dropwise addition of the solution of Compound **437b** (500 mg, 3.06 mmol) in tetrahydrofuran (10 mL). After the completion of dropwise addition, the mixture was further stirred at -78°C for 8.0 hours. The reaction mixture was quenched by adding water (1.0 mL) and a saturated aqueous ammonium chloride solution (1.0 mL), then diluted by adding water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **437c** (60 mg, 410.44 μmol, yield: 13.39%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 – 3.94 (m, 1H), 3.49 – 3.29 (m, 3H), 3.14 – 3.03 (m, 1H), 2.63 (td, J = 7.2, 14.0 Hz, 1H), 2.58 (d, J = 6.4 Hz, 2H), 1.04 (dd, J = 0.4, 6.8 Hz, 6H).

Step 3

2-(6-{1-[(5*S*)-5,6-dihydroxyl-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **437**

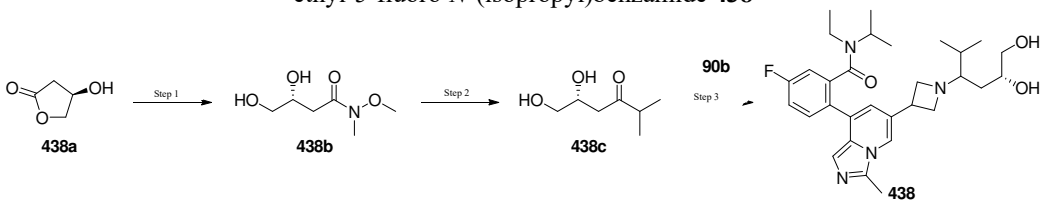
Compound **90b** (160 mg, 405.59 μmol) and Compound **437c**(59.29 mg, 405.59 μmol) were dissolved in methanol (10.0 mL), followed by the addition of $ZnCl_2$ (110.56 mg, 811.19 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (76.46 mg, 1.22 mmol) and stirring at 50°C for 11 hour. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%), to obtain the title Compound **437** (24.57 mg, 46.83 μmol, yield: 11.55%) as white solid.

MS m/z (ESI): 525.3 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.86 (m, 1H), 7.72 – 7.64 (m, 1H), 7.42 – 7.28 (m, 2H), 7.05 – 7.00 (m, 1H), 6.82 – 6.69 (m, 1H), 4.59 – 4.21 (m, 2H), 3.64 – 3.38 (m, 5H), 3.30 – 2.67 (m, 6H), 2.59 (s, 3H), 2.30 (br s, 1H), 1.92 – 1.69 (m, 1H), 1.48 – 0.95 (m, 3H), 0.93 – 0.72 (m, 12H), 0.29 (dd, J = 6.8, 13.2 Hz, 2H).

Example 438

2-(6-{1-[(5*R*)-5,6-dihydroxyl-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **438**



Step 1

(3*R*)-3,4-dihydroxyl-*N*-methoxy-*N*-methylbutyramide **438b**

N-methoxymethylamine (3.73 g, 38.20 mmol, hydrochloride) was dissolved in dichloromethane (45 mL), and cooled to 0°C under the protection of nitrogen, followed by the slow dropwise addition of $AlMe_3$ (2.0 M, 19.10 mL). After the completion of dropwise addition, the mixture was further stirred at 0°C for 0.5 hours. Under the protection of nitrogen, the mixture was cooled to -10°C, followed by the slow dropwise addition of the solution of (4*R*)-4-

hydroxyltetrahydrofuran-2-one **438a** (1.3 g, 12.73 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3.0 hours. The reaction mixture was quenched by adding sodium sulfate decahydrate while being cooled in an ice-water bath, and stirred for 1.0 hour. The mixture was filtered, and the filtrate was dried over anhydrous sodium sulfate and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **438b** (970 mg, 5.94 mmol, yield: 46.68%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.62 (d, J = 5.2 Hz, 1H), 4.57 (t, J = 5.6 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.65 (s, 3H), 3.33 – 3.22 (m, 2H), 3.08 (s, 3H), 2.48 – 2.38 (m, 2H).

Step 2

(5*R*)-5,6-dihydroxyl-2-methylhexan-3-one **438c**

Under the protection of nitrogen, Compound **438b**(410 mg, 2.51 mmol) was dissolved in tetrahydrofuran (10 mL), and cooled to -78°C under the protection of nitrogen, followed by the slow dropwise addition of an isopropyllithium solution (1.0 M, 7.54 mL). After the completion of dropwise addition, the mixture was further stirred at -78°C for 8.0 hours. The reaction mixture was quenched by adding water (1.0 mL) and a saturated aqueous ammonium chloride solution (1.0 mL), then diluted by adding water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **438c** (35 mg, 239.42 μmol, yield: 9.53%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 – 3.94 (m, 1H), 3.46 – 3.32 (m, 2H), 3.26 – 3.04 (m, 1H), 2.63 (td, J = 6.9, 13.9 Hz, 1H), 2.58 (d, J = 6.0 Hz, 2H), 1.04 (dd, J = 0.8, 7.2 Hz, 6H).

Step 3

2-(6-{1-[(5*R*)-5,6-dihydroxyl-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **438**

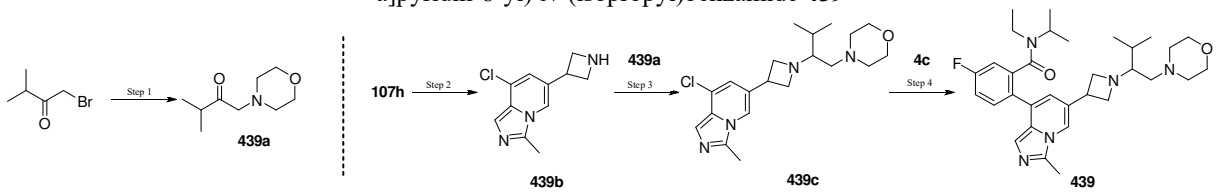
Compound **90b** (119 mg, 301.66 μmol) and Compound **438c**(35 mg, 239.42 μmol) were dissolved in methanol (10.0 mL), followed by the addition of $ZnCl_2$ (82.23 mg, 603.32 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (56.87 mg, 904.98 μmol) and stirring at 50°C for 11 hours. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (100 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **438** (35.13 mg, 66.96 μmol, yield: 22.2%) as white solid.

MS m/z (ESI): 525.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.89 (m, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.28 (m, 2H), 7.18 – 7.00 (m, 1H), 6.81 – 6.70 (m, 1H), 4.55 – 4.21 (m, 2H), 3.65 – 3.39 (m, 5H), 3.28 – 3.03 (m, 4H), 2.96 – 2.82 (m, 1H), 2.60 (s, 3H), 2.36 – 2.25 (m, 1H), 1.85 – 1.69 (m, 1H), 1.47 – 1.17 (m, 3H), 1.13 – 1.03 (m, 1H), 0.92 – 0.75 (m, 12H), 0.33 – 0.26 (m, 2H).

Example 439

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[3-methyl-1-(morpholin-4-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **439**



Step 1

3-methyl-1-(morpholin-4-yl)butan-2-one **439a**

Morpholine (500 mg, 5.74 mmol) was dissolved in acetonitrile (10 mL), followed by the addition of 1-bromo-3-methyl-but-2-one (947.13 mg, 5.74 mmol) and potassium carbonate (2.38 g, 17.22 mmol) at 25°C. The reaction mixture was heated to 80°C and stirred for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with ethyl acetate (20 mL x 3). The organic phases were combined, washed with water (20 mL x 3), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **439a** (930 mg, 5.46 mmol, yield: 95.18%) as yellow oil.

MS m/z (ESI): 282.1 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 – 3.56 (m, 4H), 3.27 (s, 2H), 2.73 (td, J = 6.9, 13.8 Hz, 1H), 2.41 – 2.36 (m, 4H), 0.99 (d, J = 6.9 Hz, 6H).

Step 2

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutane **439b**

Compound **107h** (330 mg, 1.03 mmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (20 mL), regulating to pH = 11 with a 10% aqueous sodium hydroxide solution, and extracting with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **439b** (200 mg, 902.18 μmol, yield: 87.98%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

Step 3

4-[2-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-3-methylbutyl]morpholine **439c**

Compound **439b** (220 mg, 992.40 μmol) and Compound **439a**(186.93 mg, 1.09 mmol) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (270.53 mg, 1.98 mmol), and the mixture was stirred at 50°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (187.09 mg, 2.98 mmol) and stirring at 50°C for 12 hour. A saturated aqueous sodium bicarbonate solution (50 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **439c** (90 mg, 238.78 μmol, yield: 24.06%).

MS m/z (ESI): 377.3 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[3-methyl-1-(morpholin-4-yl)butan-2-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **439**

Compound **439c** (130 mg, 344.90 μmol), Compound **4c**(138.74 mg, 413.88 μmol) and potassium phosphate (219.63 mg, 1.03 mmol) were dissolved in dioxane (2.0 mL) and water (0.5 mL). $Pd(dtbpf)Cl_2$ (22.48 mg, 34.49 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 4%-34%), to obtain the title Compound **439** (13.14 mg, 23.90 μmol, yield: 6.93%) as white solid.

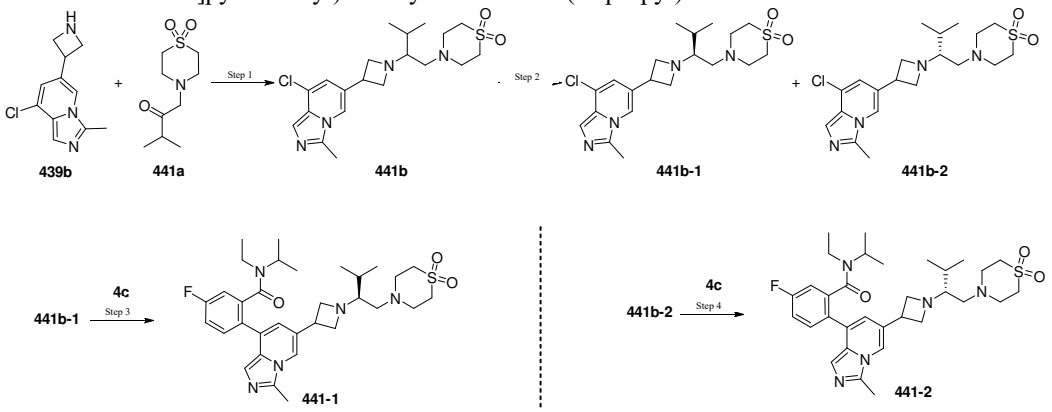
MS m/z (ESI): 550.3

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.69 (d, J = 6.4 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.18 – 7.04 (m, 2H), 6.82 – 6.77 (m, 1H), 6.60 – 6.53 (m, 1H), 3.42 – 3.35 (m, 3H), 3.20 – 3.04 (m, 6H), 3.01 – 2.97 (m, 1H), 2.93 – 2.88 (m, 1H), 2.74 – 2.64 (m, 1H), 2.38 – 2.31 (m, 3H), 2.21 – 2.13 (m, 2H), 2.11 – 2.02 (m, 3H), 1.96 – 1.90 (m, 2H), 1.58 – 1.46 (m, 1H), 0.70 – 0.60 (m, 6H), 0.60 – 0.51 (m, 6H), 0.50 – 0.45 (m, 1H), 0.04 - -0.01 (m, 2H).

Examples 441-1 and 441-2

2-(6-{1-[(2*S*)-1-(1,1-dioxo-thiomorpholin-4-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro- *N*-(isopropyl)benzamide **441-1**

2-(6-{1-[(2*R*)-1-(1,1-dioxo-thiomorpholin-4-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro- *N*-(isopropyl)benzamide **441-2**



Step 1

4-[2-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-3-methylbutyl]-thiomorpholin-1,1-dione **441b**

Compound **439b** (230 mg, 1.04 mmol) and 4-(3-methyl-2-oxobutyl)thiomorpholin-1,1-dione **441a** (250.28 mg, 1.14

mmol, synthesized with reference to the synthesis route of Compound **439a** by taking thiomorpholin-1,1-dione as a starting material) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (282.82 mg, 2.08 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (195.60 mg, 3.11 mmol) and stirring at 50°C for 8.0 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **441b** (280 mg, 658.84 μmol, yield: 63.50%).

MS m/z (ESI): 425.2 [M+1]

Step 2

4-[(2*S*)-2-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-3-methylbutyl]-thiomorpholin-1,1-dione **441b-1**

4-[(2*R*)-2-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-3-methylbutyl]-thiomorpholin-1,1-dione **441b-2**

Compound **441b**(280 mg, 658.84 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK AS(250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 50%). The title Compound **441b-1** (120 mg, 282.36 μmol, yield: 42.86%) and the title Compound **441b-2** (120 mg, 282.36 μmol, yield: 42.86%) were obtained.

Single-configuration Compound 441b-1:

MS m/z (ESI): 425.0 [M+1]

Chiral HPLC analysis: retention time: 1.882 min; chromatographic column: Chiralcel AS-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 441b-2:

MS m/z (ESI): 425.0[M+1]

Chiral HPLC analysis: retention time: 2.128 min; chromatographic column: Chiralcel AS-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

2-(6-{1-[(2*S*)-1-(1,1-dioxo-thiomorpholin-4-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro- *N*-(isopropyl)benzamide **441-1**

Compound **441b-1** (120 mg, 282.36 μmol), Compound **4c**(236.63 mg, 423.54 μmol) and potassium phosphate (179.81 mg, 847.09 μmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). $Pd(dtbpf)Cl_2$ (18.40 mg, 28.24 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, followed by adding a saturated aqueous sodium bicarbonate solution (10 mL) and extracting with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 33%-63%), to obtain the title Compound **441-1** (82.47 mg, 137.96 μmol, yield: 48.86%).

MS m/z (ESI): 598.3 [M+1]

Chiral HPLC analysis: retention time: 1.205 min; chromatographic column: Chiralcel OX-3 50 x 4.6mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.85 (m, 1H), 7.74 – 7.63 (m, 1H), 7.43 – 7.27 (m, 2H), 7.09 – 6.99 (m, 1H), 6.94 – 6.77 (m, 1H), 3.65 – 3.35 (m, 5H), 3.25 – 3.16 (m, 2H), 3.12 – 2.74 (m, 9H), 2.61 – 2.55 (m, 3H), 2.42 – 2.19 (m, 3H), 1.80 – 1.66 (m, 1H), 1.09 – 0.67 (m, 13H), 0.28 – 0.19 (m, 2H).

Step 4

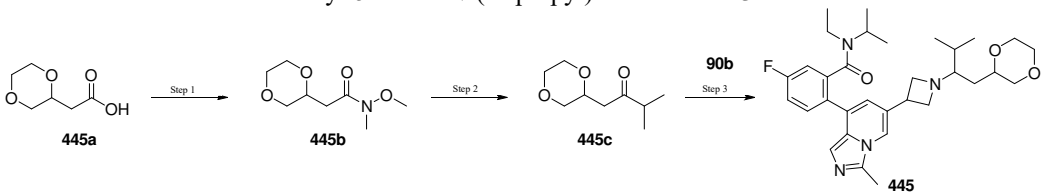
2-(6-{1-[(2*R*)-1-(1,1-dioxo-thiomorpholin-4-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro- *N*-(isopropyl)benzamide **441-2**

Compound **441b-2** (120 mg, 282.36 μmol), Compound **4c**(189.31 mg, 338.83 μmol) and potassium phosphate (179.81 mg, 847.09 μmol) were dissolved in dioxane (3.0 mL) and water (0.5 mL). $Pd(dtbpf)Cl_2$ (18.40 mg, 28.24 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, followed by adding a saturated aqueous sodium bicarbonate solution (10 mL) and extracting with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 30%-

60%), to obtain the title Compound **441-2** (83.34 mg, 139.41 μmol, yield: 49.37%).
MS m/z (ESI): 598.3 [M+1]
Chiral HPLC analysis: retention time: 2.020 min; chromatographic column: Chiralcel OX-3 50 x 4.6mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.89 (m, 1H), 7.73 – 7.64 (m, 1H), 7.42 – 7.27 (m, 2H), 7.08 – 7.00 (m, 1H), 6.94 – 6.79 (m, 1H), 3.66 – 3.36 (m, 5H), 3.26 – 3.14 (m, 2H), 3.10 – 2.72 (m, 9H), 2.63 – 2.55 (m, 3H), 2.43 – 2.18 (m, 3H), 1.81 – 1.66 (m, 1H), 1.10 – 0.68 (m, 13H), 0.28 – 0.18 (m, 2H).

Example 445

2-(6-{1-[1-(1,4-dioxane -2-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **445**



Step 1

2-(1,4-dioxane -2-yl)-*N*-methoxy-*N*-methylacetamide **445b**

2-(1,4-Dioxane -2-yl)acetic acid (500 mg, 3.42 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (1.04 g, 10.26 mmol), EDCI(787.05 mg, 4.11 mmol) and HOBT (554.77 mg, 4.11 mmol). After the reaction mixture was stirred, *N*-methoxymethylamine (367.11 mg, 3.76 mmol, hydrochloride) was added. The reaction mixture was stirred at room temperature for 3.0 hours. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (20 mL), and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **445b** (200 mg, 1.06 mmol, yield: 31%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 – 3.82 (m, 1H), 3.75 – 3.39 (m, 9H), 3.12 – 3.02 (m, 3H), 2.65 – 2.53 (m, 1H), 2.40 – 2.28 (m, 1H).

Step 2

1-(1,4-dioxane -2-yl)-3-methylbutan-2-one **445c**

Under the protection of nitrogen, Compound **445b** (200 mg, 1.06 mmol) was dissolved in tetrahydrofuran (4.0 mL), and cooled to -78°C under the protection of nitrogen, followed by the slow dropwise addition of an isopropyllithium solution (1.0 M, 3.17 mL). After the completion of dropwise addition, the mixture was further stirred at -78°C for 2.0 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (20 mL), and extracted with ethyl acetate (20 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **445c** (20 mg, 116.13 μmol, yield: 10.99%) as colorless oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 1H), 3.69 – 3.49 (m, 4H), 3.46 – 3.38 (m, 1H), 3.21 – 3.12 (m, 1H), 2.64 – 2.53 (m, 2H), 2.49 – 2.44 (m, 1H), 1.02 – 0.93 (m, 6H).

Step 3

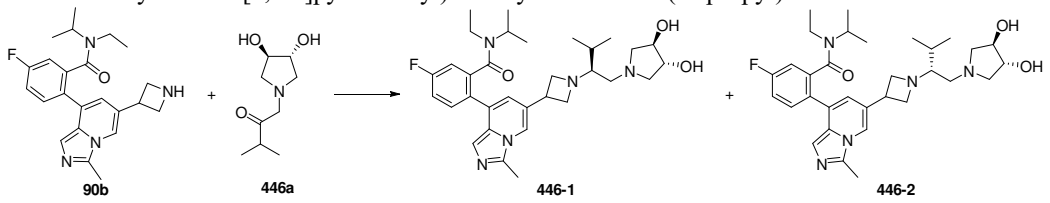
2-(6-{1-[1-(1,4-dioxane -2-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **445**

Compound **90b** (80 mg, 202.80 μmol) and Compound **445c**(45.40 mg, 263.64 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (82.92 mg, 608.39 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (38.23 mg, 608.39 μmol) and stirring at 50°C for 12 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 32%-62%), to obtain the title Compound **445** (6.9 mg, 12.53 μmol, yield: 6.18%) as white solid.
MS m/z (ESI): 551.4 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 8.00 – 7.80 (m, 1H), 7.79 – 7.55 (m, 1H), 7.50 – 6.97 (m, 3H), 6.96 – 6.75 (m, 1H), 3.83 – 3.40 (m, 11H), 3.24 – 2.95 (m, 3H), 2.73 – 2.56 (m, 3H), 2.55 – 2.39 (m, 1H), 1.99 – 1.79 (m, 1H), 1.50 – 0.76 (m, 16H), 0.34 – 0.28 (m, 2H).

Examples 446-1 and 446-2

2-(6-{1-[(2*S*)-1-[(3*R*,4*R*)-3,4-dihydroxylpyrrolidin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **446-1**

2-(6-{1-[(2*R*)-1-[(3*R*,4*R*)-3,4-dihydroxylpyrrolidin-1-yl]-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **446-2**



Compound **90b** (100 mg, 253.50 μmol) and 1-[(3*R*,4*R*)-3,4-dihydroxylpyrrolidin-1-yl]-3-methylbutan-2-one **446a** (71.20 mg, 380.24 μmol, synthesized with reference to the synthesis route of Compound **439a** by taking (3*R*,4*R*)-pyrrolidin-3,4-diol as a starting material) were dissolved in methanol (3.0 mL), followed by the addition of $ZnCl_2$ (69.10 mg, 506.99 μmol), and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (47.79 mg, 760.49 μmol) was added, and the mixture was stirred at 50°C for 48 hours. A saturated aqueous potassium carbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:24%-54%), to obtain the title Compounds **446-1** (4.67 mg, 8.25 μmol, yield: 3.26%) and **446-2** (4.52 mg, 7.99 μmol, yield: 3.15%).

Single-configuration Compound 446-1:

MS m/z (ESI): 566.4 [M+1]

Chiral HPLC analysis: retention time: 2.250 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1 H), 7.63 – 7.76 (m, 1 H), 7.27 – 7.44 (m, 2 H), 6.94 – 7.14 (m, 1 H), 6.64 – 6.90 (m, 1 H), 4.62 – 4.82 (m, 2 H), 3.79 (br d, J=4.00 Hz, 2 H), 3.58 (dt, J=13.20, 6.80 Hz, 2 H), 3.46 (br dd, J=14.40, 7.20 Hz, 2 H), 3.07 – 3.22 (m, 2 H), 2.94 (td, J=13.20, 6.40 Hz, 1 H), 2.67 – 2.86 (m, 3 H), 2.59 (s, 3 H), 2.24 – 2.33 (m, 3 H), 2.19 (br s, 2 H), 1.70 – 1.84 (m, 1 H), 0.90 (br d, J=6.40 Hz, 6 H), 0.71 – 0.86 (m, 7 H), 0.28 (br dd, J=6.00, 4.00 Hz, 2 H)

Single-configuration Compound 446-2:

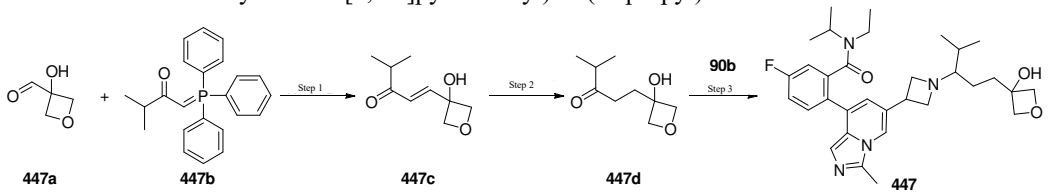
MS m/z (ESI): 566.4 [M+1]

Chiral HPLC analysis: retention time: 2.665 min; chromatographic column: Chiralcel OX-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1 H), 7.60 – 7.75 (m, 1 H), 7.24 – 7.47 (m, 2 H), 6.97 – 7.08 (m, 1 H), 6.76 (d, J=5.60 Hz, 1 H), 4.60 – 4.87 (m, 2 H), 3.79 (br d, J=4.40 Hz, 2 H), 3.57 (br d, J=5.60 Hz, 2 H), 3.46 (br dd, J=12.40, 6.00 Hz, 2 H), 3.25 (br s, 1 H), 3.06 – 3.21 (m, 2 H), 2.87 – 2.99 (m, 1 H), 2.65 – 2.83 (m, 3 H), 2.58 (s, 3 H), 2.30 – 2.39 (m, 2 H), 2.17 – 2.29 (m, 3 H), 1.75 (br d, J=6.80 Hz, 1 H), 0.89 (br d, J=6.80 Hz, 6 H), 0.72 – 0.86 (m, 7 H), 0.28 (br dd, J=8.40, 7.20 Hz, 2 H)

Example 447

N-ethyl-5-fluoro-2-(6-{1-[1-(3-hydroxyloxacyclobutan-3-yl)-4-methylpentan-3-yl]azacyclobut-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **447**



Step 1

1-(3-hydroxyloxacyclobutan-3-yl)-4-methyl-1-ene-3-one **447c**

3-Methyl-1-(triphenylphosphinidene)but-2-one **447b** (2.59 g, 7.48 mmol) was dissolved in dichloromethane (20 mL), followed by the addition of 3-hydroxyloxacyclobutan-3-formaldehyde **447a** (509 mg, 4.99 mmol). The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **447c** (371 mg, 2.18 mmol, yield: 43.72%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (d, J = 16.4 Hz, 1H), 6.44 (d, J = 15.6 Hz, 1H), 6.29 (s, 1H), 4.58 – 4.54 (m, 4H), 2.95 (td, J = 6.8, 13.6 Hz, 1H), 1.03 (d, J = 6.8 Hz, 6H).

Step 2

1-(3-hydroxyloxacyclobutan-3-yl)-4-methylpentan-3-one **447d**

Compound **447c** (371 mg, 2.18 mmol) was dissolved in ethanol (10.0 mL), followed by the addition of Pd/C (264.74 mg, 217.97 μmol, 10% purity) under the protection of argon. The reaction system was subjected to hydrogen substitution (25PSI), and stirred at 30°C to allow for reacting for 12 hours. The mixture was filtered through diatomite, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **447d** (84 mg, 487.75 μmol, yield: 22.38%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.59 (s, 1H), 4.40 – 4.28 (m, 4H), 2.70 – 2.59 (m, 1H), 2.57 – 2.53 (m, 2H), 1.92 – 1.85 (m, 2H), 1.01 (d, J = 6.9 Hz, 6H).

Step 3

N-ethyl-5-fluoro-2-(6-{1-[1-(3-hydroxyloxacyclobutan-3-yl)-4-methylpentan-3-yl]azacyclobut-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **447**

Compound **90b** (192.41 mg, 487.75 μmol) and Compound **447d**(84 mg, 487.75 μmol) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$ (132.96 mg, 975.49 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (91.95 mg, 1.46 mmol) and stirring at 50℃ for 11 hour. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 1%-30%), to obtain the title Compound **447** (20.89 mg, 37.93 μmol, yield: 7.78%) as yellow solid.

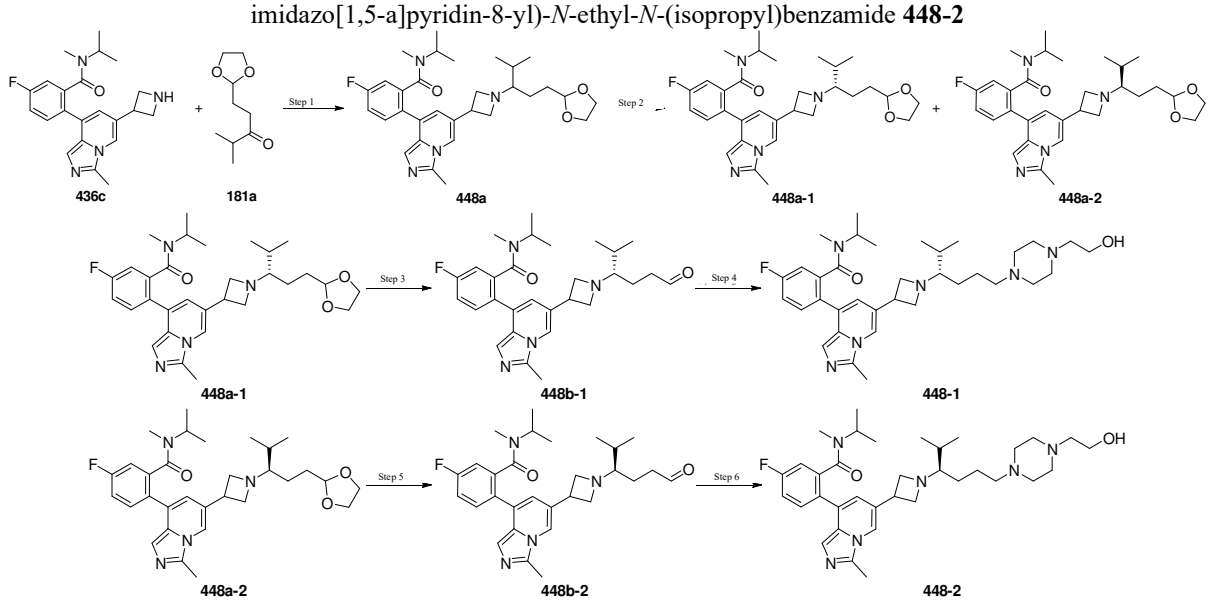
MS m/z (ESI): 551.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.64 (m, 1H), 7.42 – 7.28 (m, 2H), 7.07 – 7.01 (m, 1H), 6.87 – 6.73 (m, 1H), 5.52 (br s, 1H), 4.38 (br d, J = 5.6 Hz, 2H), 4.33 – 4.24 (m, 2H), 3.64 – 3.39 (m, 4H), 3.22 – 3.04 (m, 2H), 3.00 – 2.87 (m, 1H), 2.59 (s, 3H), 2.05 (br s, 1H), 1.85 – 1.67 (m, 3H), 1.37 – 1.20 (m, 2H), 1.09 – 0.69 (m, 14H), 0.28 (dd, J = 2.4, 6.4 Hz, 2H).

Examples 448-1 and 448-2

5-fluoro-2-(6-{1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-*N*-(isopropyl)benzamide **448-1**

5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-*N*-(isopropyl)benzamide **448-2**



Step 1

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-methyl-5-fluoro-*N*-(isopropyl)benzamide **448a**

Compound **436c** (340 mg, 893.66 μmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (230.86 mg, 1.34

mmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (243.60 mg, 1.79 mmol), and the mixture was stirred at 55°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (168.48 mg, 2.68 mmol) and stirring at 55°C for 11 hour. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **448a** (280 mg, 521.73 μmol, yield: 58.38%) as yellow solid.
MS m/z (ESI): 551.3 [M+1]

Step 2

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **448a-1**

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **448a-2**

Compound **448a** (280 mg, 521.73 μmol) was separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-ethanol (0.1% ammonia water); elution gradient: 20%), to obtain the title Compounds **448a-1** (100 mg, 186.33 μmol, yield: 35.71%) and **448a-2** (90 mg, 167.70 μmol, yield: 32.14%).

Single-configuration Compound 448a-1:
MS m/z (ESI):537.3 [M+1]
Chiral HPLC analysis: retention time: 1.137 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 448a-2:
MS m/z (ESI): 537.3 [M+1]
Chiral HPLC analysis: retention time: 1.355 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-ethanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 3

5-fluoro-*N*-methyl-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **448b-1**

Compound **448a-1** (100 mg, 186.33 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 55°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **448b-1** (80 mg, 162.39 μmol,yield: 87.15%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 448b-1:
MS m/z (ESI): 493.3 [M+1]

Step 4

5-fluoro-2-(6-{1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-*N*-(isopropyl)benzamide **448-1**

The crude product of Compound **448b-1** (80 mg, 162.39 μmol) and 2-piperazin-1-ylethanol (31.71 mg, 243.59 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (9.75 mg, 162.39 μmol), and the mixture was stirred at 35°C for 1.0 hour. Sodium cyanoborohydride (30.62 mg, 487.18 μmol) was added, allowing for reacting at 35°C for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (35 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-48%). The title Compound **448-1** (41.74 mg, 68.79 μmol, yield: 42.36%) was obtained.

Single-configuration Compound 448-1:
MS m/z (ESI):607.3 [M+1]
Chiral SFC: retention time: 1.185 min; chromatographic column: Chiralcel AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.77 – 7.66 (m, 1H), 7.44 – 7.27 (m, 2H), 7.11 – 7.02 (m, 1H), 6.87 – 6.72 (m, 1H), 4.60 (s, 7H), 3.18 – 2.97 (m, 2H), 2.79 – 2.54 (m, 5H), 2.46 – 2.16 (m, 13H), 2.09 – 1.99 (m, 1H), 1.79 – 1.63 (m, 1H), 1.56 – 1.34 (m, 2H), 1.31 – 0.56 (m, 13H), 0.24 (d, J = 6.4 Hz, 1H).

Step 5

5-fluoro-*N*-methyl-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **448b-2**

Compound **448a-2** (90 mg, 167.70 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **448b-2** (70 mg, 142.10 μmol,yield: 84.73%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 448b-2:

MS m/z (ESI): 493.3 [M+1]

Step 6

5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-*N*-(isopropyl)benzamide **448-2**

The crude product of Compound **448b-2** (70 mg, 142.10 μmol) and 2-piperazin-1-ylethanol (27.75 mg, 213.14 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (8.53 mg, 142.10 μmol), and the mixture was stirred at 35°C for 1.0 hour. Sodium cyanoborohydride (26.79 mg, 426.29 μmol) was added, allowing for reacting at 35℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (35 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-48%). The title Compound **448-2** (35.20 mg, 58.01 μmol, yield: 40.82%) was obtained as yellow solid.

Single-configuration Compound 448-2:

MS m/z (ESI):607.4 [M+1]

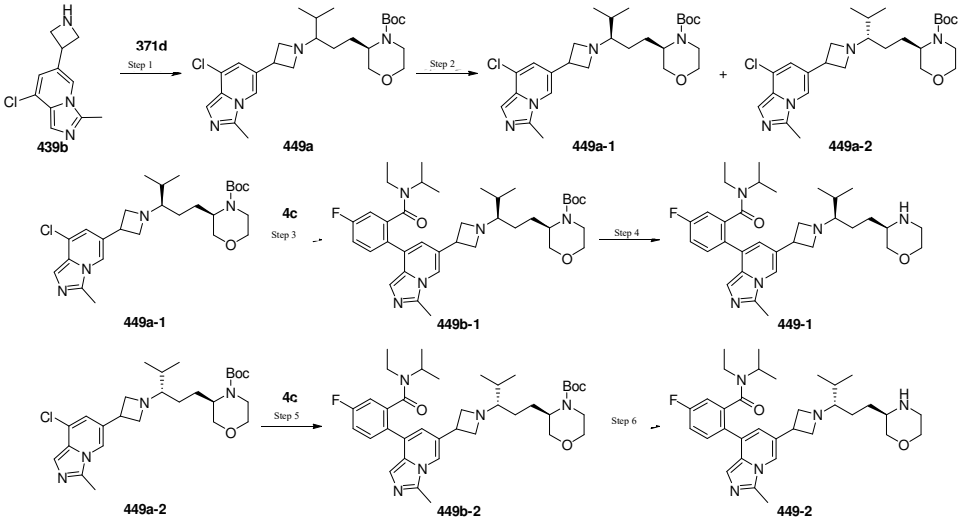
Chiral SFC: retention time: 1.117 min; chromatographic column: Chiralcel AD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.77 – 7.66 (m, 1H), 7.45 – 7.27 (m, 2H), 7.12 – 7.02 (m, 1H), 6.89 – 6.71 (m, 1H), 4.62 – 3.41 (m, 7H), 3.19 – 2.99 (m, 2H), 2.77 – 2.54 (m, 5H), 2.47 – 2.14 (m, 13H), 2.08 – 1.99 (m, 1H), 1.77 – 1.63 (m, 1H), 1.53 – 1.35 (m, 2H), 1.31 – 0.55 (m, 13H), 0.24 (d, J = 6.4 Hz, 1H).

Examples 449-1 and 449-2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **449-1**

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **449-2**



Step 1

(3*R*)-3-[3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **449a**

Compound **439b** (344 mg, 1.55 mmol) and Compound **371d**(885.67 mg, 3.10 mmol) were dissolved in methanol (10.0 mL), followed by the addition of $ZnCl_2$ (423.01 mg, 3.10 mmol), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (292.54 mg, 4.66 mmol) was added, and the mixture was stirred at 50℃ for 2.0 hours. Compound **439b** (344 mg, 1.55 mmol) was supplemented, and the mixture was further stirred at 50℃ for 12.0 hours. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then

extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 52%-82%), to obtain the title Compound **449a** (320 mg, 651.65 μmol, yield: 21%) as yellow solid.
MS m/z (ESI): 491.4 [M+1]

Step 2

(3*R*)-3-[(3*R*)-3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **449a-1**

tert-butyl (3R)-3-[(3S)-3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azetidin-1-yl)-4-methylpentyl]morpholine-4-carboxylate

(3*R*)-3-[(3*S*)-3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **449a-2**

Compound **449a** (320 mg, 651.65 μmol) was purified by the chiral preparative SFC (preparative column: Column: DAICEL CHIRALCEL OD(250 mm * 30 mm,10 um), mobile phase: carbon dioxide-methanol (0.1% ammonia water); elution gradient: 15%). The title Compound **449a-1** (216 mg, 439.86 μmol) and the title Compound **449a-2** (80 mg, 162.91 μmol) were obtained.

Single-configuration Compound 449a-1:

MS m/z (ESI): 491.4 [M+1]
Chiral HPLC analysis: retention time: 1.146 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.34 (s, 1H), 7.06 (s, 1H), 3.92 – 3.69 (m, 6H), 3.67 – 3.57 (m, 1H), 3.53 (dd, J = 3.2, 11.6 Hz, 1H), 3.45 – 3.34 (m, 3H), 2.65 (s, 3H), 2.24 (s, 1H), 2.07 – 1.54 (m, 4H), 1.48 – 1.43 (m, 9H), 1.39 – 1.10 (m, 2H), 1.02 – 0.85 (m, 6H).

Single-configuration Compound 449a-2:

MS m/z (ESI): 491.5 [M+1]
Chiral HPLC analysis: retention time: 1.203 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.35 (s, 1H), 7.06 (s, 1H), 3.83 – 3.73 (m, 6H), 3.68 – 3.61 (m, 1H), 3.54 (dd, J = 3.2, 11.8 Hz, 1H), 3.41 (dt, J = 2.8, 11.9 Hz, 3H), 2.65 (s, 3H), 2.03 (s, 1H), 1.91 – 1.72 (m, 4H), 1.47 – 1.45 (m, 9H), 1.35 (td, J = 2.6, 5.3 Hz, 2H), 0.95 (dd, J = 6.8, 15.4 Hz, 6H).

Step 3

(3*R*)-3-[(3*R*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **449b-1**

Compound **449a-1** (216 mg, 439.86 μmol), Compound **4c** (203.38 mg, 527.83 μmol) and potassium phosphate (280.1 mg, 1.32 mmol) were dissolved in dioxane (16 mL) and water (4 mL). Pd(dtbpf)Cl_2 (18.92 mg, 21.99 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **449b-1** (158 mg, 238.00 μmol, yield: 54.11%) as yellow oil.
MS m/z (ESI): 664.5 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **449-1**

Compound **449b-1** (158 mg, 238.00 μmol) was dissolved in dichloromethane (15 mL), followed by the addition of trifluoroacetic acid (4.44 g, 38.94 mmol, 3 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to PH >7 with a 10% aqueous sodium hydroxide solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 28%-58%), to obtain the title Compound **449-1** (81.07 mg, 143.81 μmol, yield: 60.42%) as yellow solid.
MS m/z (ESI): 564.4 [M+1]
Chiral HPLC analysis: retention time: 1.115 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.94 – 7.87 (m, 1H), 7.77 – 7.67 (m, 1H), 7.38 – 7.30 (m, 1H), 7.29 – 7.19 (m, 1H),

7.18 – 7.09 (m, 1H), 6.97 – 6.85 (m, 1H), 3.83 – 3.36 (m, 8H), 3.30 – 3.20 (m, 2H), 3.18 – 2.97 (m, 2H), 2.92 – 2.78 (m, 2H), 2.73 – 2.61 (m, 4H), 2.21 (s, 1H), 1.91 – 1.79 (m, 1H), 1.58 – 1.08 (m, 5H), 1.07 – 0.69 (m, 13H), 0.33 – 0.27 (m, 2H).

Step 5

(3*R*)-3-[(3*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **449b-2**

Compound **449a-2** (80 mg, 162.91 μmol), Compound **4c**(75.33 mg, 195.49 μmol) and potassium phosphate (103.74 mg, 488.73 μmol) were dissolved in dioxane (16 mL) and water (4 mL). $Pd(dtbpf)Cl_2$ (7.01 mg, 8.15 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 16 hours. The reaction mixture was cooled to room temperature, followed by the addition of water (50 mL) and extraction with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **449b-2** (74 mg, 111.47 μmol, yield: 68.42%).

MS m/z (ESI): 664.6 [M+1]

Step 6

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **449-2**

Compound **449b-2** (80 mg, 120.51 μmol) was dissolved in dichloromethane (1.0 mL), followed by the addition of trifluoroacetic acid (13.74 mg, 120.51 μmol, 9.28 μL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour, and the reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to PH >7 with a 10% aqueous sodium hydroxide solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%), to obtain the title Compound **449-2** (15.68 mg, 27.81 μmol, yield: 23.08%) as yellow solid.

MS m/z (ESI): 564.5 [M+1]

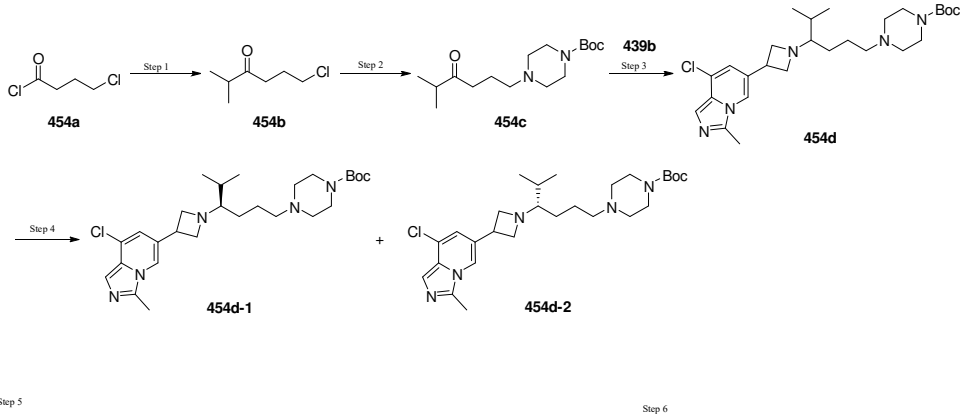
Chiral HPLC analysis: retention time: 1.113 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, CD_3OD) δ 7.93 – 7.89 (m, 1H), 7.76 – 7.68 (m, 1H), 7.39 – 7.30 (m, 1H), 7.28 – 7.20 (m, 1H), 7.17 – 7.10 (m, 1H), 6.97 – 6.84 (m, 1H), 3.81 – 3.64 (m, 5H), 3.38 (s, 3H), 3.29 – 3.21 (m, 2H), 3.19 – 2.98 (m, 2H), 2.89 – 2.79 (m, 2H), 2.72 – 2.62 (m, 4H), 2.25 – 2.16 (m, 1H), 1.93 – 1.78 (m, 1H), 1.58 – 1.45 (m, 1H), 1.44 – 1.11 (m, 5H), 0.97 – 0.89 (m, 11H), 0.80 (t, J = 7.0 Hz, 1H), 0.32 – 0.28 (m, 2H).

Examples 454-1 and 454-2

4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454-1**

4-[(4*S*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454-2**



Step 2

6-chloro-2-methylhexan-3-one **454b**

4-Chlorobutyryl chloride **454a** (10 g, 70.92 mmol) was dissolved in tetrahydrofuran (100 mL), and cooled to 0°C under the protection of nitrogen, followed by the slow dropwise addition of an isopropylmagnesium chloride solution (2.0 M, 35.46 mL). After dropwise addition, the mixture was slowly warmed to 25°C and stirred for 12.0 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (100 mL), and extracted with ethyl acetate (50 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **454b** (4.0 g, 26.91 mmol, yield: 37.95%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 – 3.56 (m, 2H), 2.70 – 2.58 (m, 3H), 2.09 – 2.01 (m, 2H), 1.12 (d, J = 7.0 Hz, 6H).

Step 2

4-(5-methyl-4-oxohexyl)piperazin-1-tert-butyl carboxylate **454c**

Compound **454b** (4.0 g, 26.91 mmol) was dissolved in acetonitrile (60 mL), followed by the addition of piperazin-1-tert-butyl carboxylate (6.01 g, 32.29 mmol), potassium carbonate (7.44 g, 53.82 mmol) and sodium iodide (403.40 mg, 2.69 mmol) at 25°C. The reaction mixture was heated to 85°C and stirred for 12 hours. The reaction mixture was cooled to room temperature, filtered, and washed with ethyl acetate (50 mL x 3). The organic phases were combined and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **454c** (4 g, 13.40 mmol, yield: 49.81%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 – 3.39 (m, 4H), 2.61 (br d, J = 6.9 Hz, 1H), 2.48 (t, J = 7.1 Hz, 2H), 2.38 – 2.31 (m, 6H), 1.81 – 1.74 (m, 2H), 1.45 (s, 9H), 1.09 (d, J = 6.9 Hz, 6H).

Step 3

4-[4-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454d**

Compound **439b** (2 g, 9.02 mmol) and Compound **454c** (2.96 g, 9.92 mmol) were dissolved in methanol (20.0 mL), followed by the addition of $ZnCl_2$ (3.69 g, 27.07 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (1.70 g, 27.07 mmol) and stirring at 50°C for 12.0 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **454d** (3.4 g, 6.74 mmol, yield: 74.76%) as yellow solid.

MS m/z (ESI): 504.3 [M+1]

Step 4

4-[(4*R*)-4-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454d-1**

tert-butyl 4-[(4S)-4-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azetidin-1-yl)-5-methylhexyl]piperazine-1-carboxylate

4-[(4*S*)-4-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454d-2**

Compound **454d**(3.4 g, 6.74 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD(250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 30%). The title Compounds **454d-1** (1.65 g, 3.27 mmol, yield: 48.53%) and **454d-2** (1.6 g, 3.17 mmol, yield: 47.06%) were obtained as yellow solid.

Single-configuration Compound 454d-1:

MS m/z (ESI): 504.2 [M+1]

Chiral HPLC analysis: retention time: 1.446 min; chromatographic column: Chiralcel AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 454d-2:

MS m/z (ESI): 504.3 [M+1]

Chiral HPLC analysis: retention time: 1.645 min; chromatographic column: Chiralcel AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 5

4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454-1**

Compound **454d-1** (1.65 g, 3.27 mmol), Compound **4c** (1.51 g, 3.93 mmol) and potassium phosphate (2.08 g, 9.82

mmol) were dissolved in dioxane (15 mL) and water (3 mL). $Pd(dtbpf)Cl_2$ (106.66 mg, 163.66 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **454-1** (1.8 g, 2.66 mmol, yield: 81.24%).

MS m/z (ESI): 677.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 7.79 (m, 1H), 7.78 – 7.53 (m, 1H), 7.49 – 7.17 (m, 2H), 7.16 – 6.88 (m, 1H), 6.88 – 6.66 (m, 1H), 3.62 – 3.36 (m, 4H), 3.29 – 2.87 (m, 8H), 2.64 – 2.53 (m, 3H), 2.32 – 2.17 (m, 6H), 2.07 – 1.99 (m, 1H), 1.80 – 1.62 (m, 1H), 1.59 – 1.09 (m, 14H), 1.08 – 0.69 (m, 13H), 0.30 – 0.23 (m, 2H).

Step 6

4-[(4*S*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **454-2**

Compound **454d-2** (1.60 g, 3.17 mmol), Compound **4c** (1.47 g, 3.81 mmol) and potassium phosphate (2.02 g, 9.52 mmol) were dissolved in dioxane (16 mL) and water (4 mL). $Pd(dtbpf)Cl_2$ (136.55 mg, 158.70 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **454-2** (2.0 g, 2.96 mmol, yield: 93.23%).

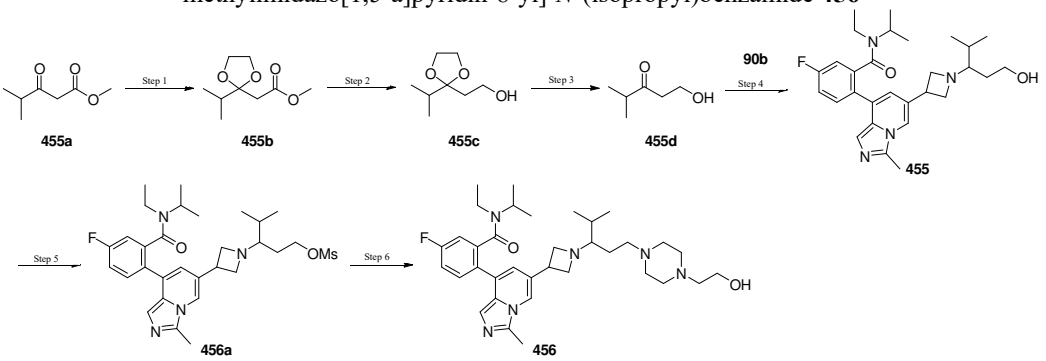
MS m/z (ESI): 677.5 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.79 (m, 1H), 7.75 – 7.56 (m, 1H), 7.46 – 7.21 (m, 2H), 7.14 – 6.87 (m, 1H), 6.87 – 6.63 (m, 1H), 3.70 – 3.36 (m, 4H), 3.29 – 2.87 (m, 8H), 2.65 – 2.54 (m, 3H), 2.30 – 2.17 (m, 6H), 2.06 – 1.99 (m, 1H), 1.77 – 1.62 (m, 1H), 1.52 – 1.13 (m, 14H), 1.09 – 0.70 (m, 13H), 0.29 – 0.24 (m, 2H).

Examples 455 and 456

N-ethyl-5-fluoro-2-{6-[1-(1-hydroxyl-4-methylpentan-3-yl)azacyclobutan-3-yl]-3-methylimidazo[1,5-a]pyridin-8-yl}-*N*-(isopropyl)benzamide **455**

N-ethyl-5-fluoro-2-[6-(1-{1-[4-(2-hydroxyethyl)piperazin-1-yl]-4-methylpentan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **456**



Step 1

2-(1,4-dioxane -2-yl)-*N*-methoxy-*N*-methylacetamide **445b**

2-(1,4-Dioxane -2-yl)acetic acid (500 mg, 3.42 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (1.04 g, 10.26 mmol), EDCI(787.05 mg, 4.11 mmol) and HOBT (554.77 mg, 4.11 mmol). After the reaction mixture was stirred, *N*-methoxymethylamine (367.11 mg, 3.76 mmol, hydrochloride) was added. The reaction mixture was stirred at room temperature for 3.0 hours. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (20 mL), and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **445b** (200 mg, 1.06 mmol, yield: 31%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 – 3.82 (m, 1H), 3.75 – 3.39 (m, 9H), 3.12 – 3.02 (m, 3H), 2.65 – 2.53 (m, 1H), 2.40 – 2.28 (m, 1H).

Step 2

1-(1,4-dioxane -2-yl)-3-methylbutan-2-one **445c**

Under the protection of nitrogen, Compound **445b** (200 mg, 1.06 mmol) was dissolved in tetrahydrofuran (4.0 mL), and cooled to -78°C under the protection of nitrogen, followed by the slow dropwise addition of an isopropyllithium

solution (1.0 M, 3.17 mL). After the completion of dropwise addition, the mixture was further stirred at -78℃ for 2.0 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (20 mL), and extracted with ethyl acetate (20 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **445c** (20 mg, 116.13 μmol, yield: 10.99%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 1H), 3.69 – 3.49 (m, 4H), 3.46 – 3.38 (m, 1H), 3.21 – 3.12 (m, 1H), 2.64 – 2.53 (m, 2H), 2.49 – 2.44 (m, 1H), 1.02 – 0.93 (m, 6H).

Step 3

2-(6-{1-[1-(1,4-dioxane -2-yl)-3-methylbutan-2-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **445**

Compound **90b** (80 mg, 202.80 μmol) and Compound **445c**(45.40 mg, 263.64 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (82.92 mg, 608.39 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (38.23 mg, 608.39 μmol) and stirring at 50℃ for 12 hours. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 32%-62%), to obtain the title Compound **445** (6.9 mg, 12.53 μmol, yield: 6.18%) as white solid.

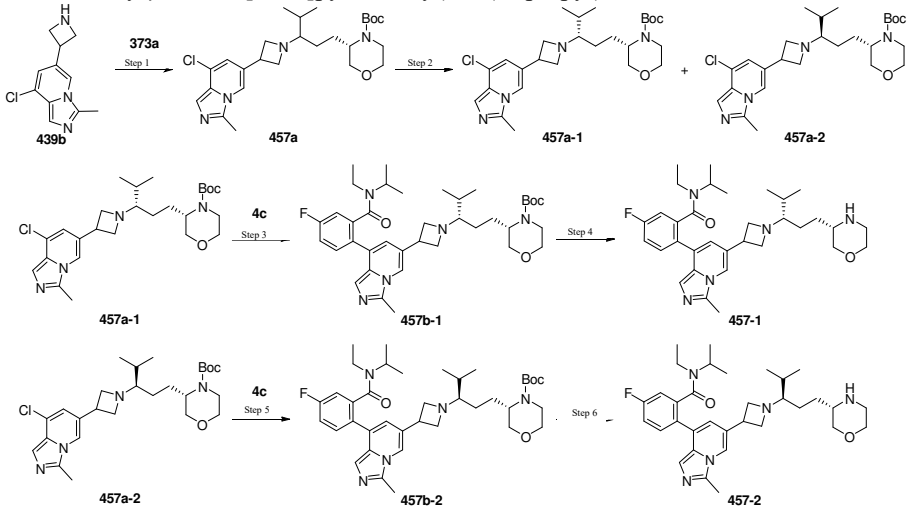
MS m/z (ESI): 551.4 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.00 – 7.80 (m, 1H), 7.79 – 7.55 (m, 1H), 7.50 – 6.97 (m, 3H), 6.96 – 6.75 (m, 1H), 3.83 – 3.40 (m, 11H), 3.24 – 2.95 (m, 3H), 2.73 – 2.56 (m, 3H), 2.55 – 2.39 (m, 1H), 1.99 – 1.79 (m, 1H), 1.50 – 0.76 (m, 16H), 0.34 – 0.28 (m, 2H).

Examples 457-1 and 457-2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **457-1**

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **457-2**



Step 1

(3*S*)-3-[3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **457a**

Compound **439b** (380 mg, 1.71 mmol) and Compound **373a** (489.18 mg, 1.71 mmol) were dissolved in methanol (10.0 mL), followed by the addition of $ZnCl_2$ (467.27 mg, 3.43 mmol), and the mixture was stirred at 50°C for 1.0 hour. Sodium cyanoborohydride (323.16 mg, 5.14 mmol) was added, and the mixture was stirred at 50℃ for 2.0 hours. A saturated aqueous potassium carbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified

by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 10%-29%), to obtain the title Compound **457a** (210 mg, 101.82 μmol, yield: 5.94%) as white solid.
MS m/z (ESI): 491.1 [M+1]

Step 2

(3*S*)-3-[(3*S*)-3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **457a-1**

(3*S*)-3-[(3*R*)-3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholin-4-tert-butyl carboxylate **457a-2**

Compound **457a** was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK IG (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 40%). Mixtures **B** (MS m/z (ESI): 491.2 [M+1], Chiral HPLC analysis: retention time: 2.543 min; chromatographic column: Chiralpak AD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%) and **A** (MS m/z (ESI): 491.2 [M+1], Chiral HPLC analysis: retention time: 2.543 min; chromatographic column: (S,S)Whelk-O1 50 x 4.6 mm I.D., 3.5 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%) were obtained. The mixture B was further separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 30%), to obtain the title Compound **457a-1** (110 mg); and the mixture A was further separated and purified by the chiral preparative HPLC (preparative column: DAICEL CHIRALPAK ID (250 mm * 30mm,10 um), mobile phase: n-hexane-isopropanol (0.1% ammonia water); elution gradient: 15%), to obtain the title Compound **457a-2** (100 mg).

Single-configuration Compound 457a-1:
MS m/z (ESI): 491.2 [M+1]
Chiral HPLC analysis: retention time: 1.418 min; chromatographic column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.05% diethylamide); elution gradient: 5%-40%.

Single-configuration Compound 457a-2:
MS m/z (ESI): 491.2 [M+1]
Chiral HPLC analysis: retention time: 2.784 min; chromatographic column: Chiralpak ID-3 50 x 4.6 mm I.D., 3 um; mobile phase: n-hexane-isopropanol (0.05% isopropylamine): elution gradient: 10%.

Step 3

(3*S*)-3-[(3*S*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **457b-1**

Compound **457a-1** (110 mg, 224 μmol), Compound **4c**(225.27 mg, 672.01 μmol) and potassium phosphate (142.65 mg, 672.01 μmol) were dissolved in dioxane (2.0 mL) and water (0.5 mL). Pd(dtbpf)Cl_2 (14.60 mg, 22.40 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 100°Cto allow for reacting for 16 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **457b-1** (160 mg, 241.01 μmol, yield: 107.59%) as brown oil.
MS m/z (ESI): 664.5 [M+1]

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **457-1**

Compound **457b-1** (160.00 mg, 241.01 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 0%-22%), to obtain the title Compound **457-1** (69.52 mg, 123.32 μmol, yield: 51.17%) as green solid.
MS m/z (ESI): 564.3 [M+1]
Chiral HPLC analysis: retention time: 1.113 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 – 10.14 (m, 2 H), 8.09 (br s, 1 H), 7.63 – 7.72 (m, 1 H), 7.40 (td, J=8.40, 2.40 Hz, 1 H), 7.34 (br d, J=8.40 Hz, 1 H), 7.05 – 7.11 (m, 1 H), 6.72 – 6.84 (m, 1 H), 4.05 – 4.27 (m, 2 H), 3.76 – 4.00 (m, 5 H), 3.61 (br t, J=11.20 Hz, 1 H), 3.41 – 3.48 (m, 2 H), 3.22 (br s, 3 H), 3.00 – 3.11 (m, 2 H), 2.88 (br dd, J=13.60, 6.80 Hz, 1 H), 2.61 (s, 3 H), 1.91 (br d, J=1.20 Hz, 1 H), 1.47 – 1.61 (m, 4 H), 0.85 – 0.98 (m, 10 H), 0.71 – 0.77 (m, 3 H), 0.26 (br d, J=6.00 Hz, 2 H).

Step 5

(3*S*)-3-[(3*R*)-3-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-4-methylpentyl]morpholin-4-tert-butyl carboxylate **457b-2**

Compound **457a-2** (100 mg, 203.64 μmol), Compound **4c**(273.06 mg, 814.56 μmol) and potassium phosphate (129.68 mg, 610.92 μmol) were dissolved in dioxane (2.0 mL) and water (0.5 mL). Pd(dtbpf)Cl_2 (7.01 mg, 8.15 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 16 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **457b-2** (110 mg, 165.70 μmol, yield: 81.37%).
MS m/z (ESI): 664.6 [M+1]

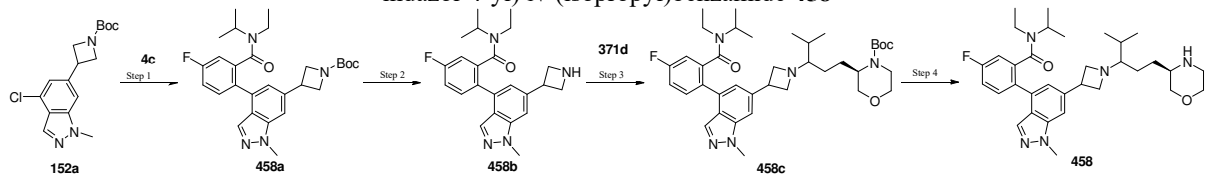
Step 6

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-4-methyl-1-[(3*S*)-morpholin-3-yl]pentan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **457-2**

Compound **457b-2** (110 mg, 165.70 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 0%-27%), to obtain the title Compound **457-2** (64.25 mg, 113.97 μmol, yield: 68.78%) as green solid.
MS m/z (ESI): 564.3 [M+1]
Chiral HPLC analysis: retention time: 1.112 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 – 9.71 (m, 2 H), 8.05 – 8.27 (m, 1 H), 7.60 – 7.83 (m, 1 H), 7.26 – 7.51 (m, 2 H), 7.04 – 7.19 (m, 1 H), 6.80 (br d, J=11.20 Hz, 1 H), 4.07 – 4.55 (m, 4 H), 3.85 – 4.03 (m, 3 H), 3.63 (br t, J=11.60 Hz, 1 H), 3.41 – 3.49 (m, 2 H), 3.02 – 3.30 (m, 5 H), 2.89 (br dd, J=12.80, 5.60 Hz, 1 H), 2.63 (s, 3 H), 2.01 (br s, 1 H), 1.43 – 1.76 (m, 4 H), 0.80 – 1.15 (m, 10 H), 0.68 – 0.78 (m, 3 H), 0.28 (br d, J=6.00 Hz, 2 H).

Example 458

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **458**



Step 1

3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-tert-butyl carboxylate **458a**

Compound **152a** (1 g, 3.11 mmol), Compound **4c**(1.04 g, 3.11 mmol) and potassium phosphate (1.65 g, 7.77 mmol) were dissolved in dioxane (10 mL) and water (2 mL). Xphos-Pd-G4 (267.39 mg, 310.75 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **458a** (800 mg, 1.62 mmol, yield: 52.05%) as brown solid.
MS m/z (ESI): 495.2 [M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-1-methyl-1*H*-indazol-4-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **458b**

Compound **458a** (150 mg, 303.28 μmol) was dissolved in dichloromethane (6.0 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to PH >7 with a 10% aqueous sodium hydroxide solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 28%-58%), to obtain the title Compound **458b** (119 mg, 301.66 μmol, yield: 99.47%) as black solid. The crude product was directly used in the next step of reaction without purification.

Step 3

(3*R*)-3-{3-[3-(4-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methyl-1*H*-indazol-6-yl)azacyclobutan-1-yl]-4-methylpentyl}morpholin-4-tert-butyl carboxylate **458c**

Compound **458b** (119 mg, 301.66 μmol) and Compound **371d**(103.30 mg, 361.99 μmol) were dissolved in methanol (5.0 mL), followed by the addition of $ZnCl_2$ (82.23 mg, 603.32 μmol), and the mixture was stirred at 50°C for 1.0

hour. Sodium cyanoborohydride (37.91 mg, 603.32 μmol) was added, and the mixture was stirred at 50℃ for 2.0 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **458c** (120 mg, 180.76 μmol, yield: 59.92%) as yellow oil.
MS m/z (ESI): 664.4 [M+1]

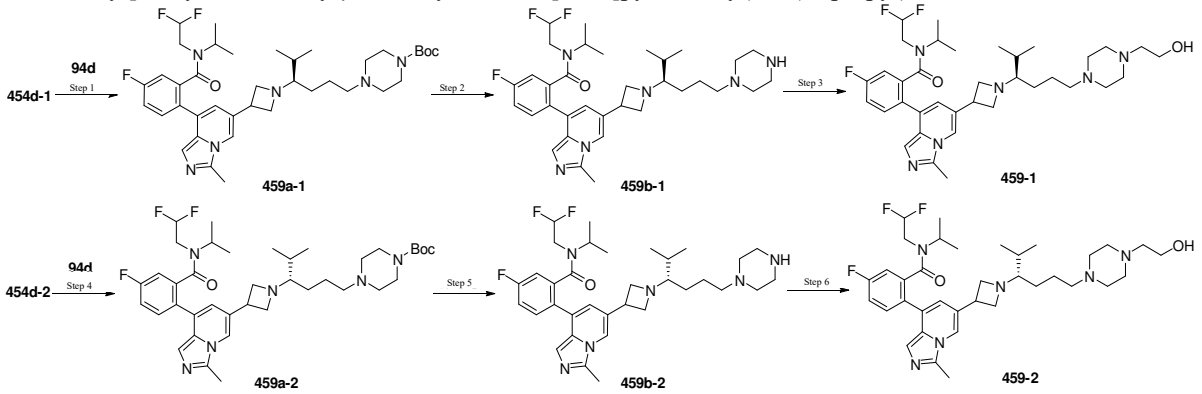
Step 4

N-ethyl-5-fluoro-2-[1-methyl-6-(1-{4-methyl-1-[(3*R*)-morpholin-3-yl]pentan-3-yl}azacyclobutan-3-yl}-1*H*-indazol-4-yl)-*N*-(isopropyl)benzamide **458**

Compound **458c** (120.00 mg, 180.76 μmol) was dissolved in dichloromethane (6 mL), followed by the addition of trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to PH >7 with a 10% aqueous sodium hydroxide solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 35%-65%), to obtain the title Compound **458** (68.61 mg, 121.70 μmol, yield: 67.33%) as white solid.
MS m/z (ESI): 564.3 [M+1]
^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (s, 1H), 7.67 – 7.61 (m, 1H), 7.52 – 7.46 (m, 1H), 7.35 (dt, J = 2.8, 8.4 Hz, 1H), 7.27 – 7.14 (m, 2H), 4.09 (s, 3H), 3.91 – 3.74 (m, 5H), 3.53 – 3.36 (m, 3H), 3.19 – 3.10 (m, 1H), 2.98 – 2.79 (m, 3H), 2.73 – 2.64 (m, 1H), 2.26 – 2.17 (m, 1H), 1.94 – 1.81 (m, 1H), 1.60 – 1.15 (m, 5H), 1.10 – 0.88 (m, 10H), 0.84 – 0.69 (m, 4H), 0.10 (d, J = 6.4 Hz, 2H).

Examples 459-1 and 459-2

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459-1**
N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[(3*S*)- 6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459-2**



Step 1

4-[(4*R*)-4-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **459a-1**

Compound **454d-1** (200.00 mg, 396.74 μmol), Compound **94d**(176.73 mg, 476.09 μmol) and potassium phosphate (252.64 mg, 1.19 mmol) were dissolved in dioxane (5 mL) and water (1 mL). Xphos-Pd-G4 (34.14 mg, 39.67 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **459a-1** (170 mg, 238.47 μmol, yield: 60.11%).
MS m/z (ESI): 713.4 [M+1]

Step 2

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(piperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459b-1**

Compound **459a-1**(170.00 mg, 238.47 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition

of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **459b-1** (140 mg, 228.47 μmol, yield: 95.81%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 613.4 [M+1]

Step 3

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459-1**

The crude product of Compound **459b-1** (140.00 mg, 228.47 μmol) was dissolved in acetonitrile (3.0 mL), followed by the addition of 2-bromoethanol (34.26 mg, 274.16 μmol) and potassium carbonate (94.73 mg, 685.41 μmol), and the mixture was stirred at 80°C for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 34%-54%). The title Compound **459-1** (25.25 mg, 38.44 μmol, yield: 16.83%) was obtained.

Single-configuration Compound 459-1:

MS m/z (ESI):657.5 [M+1]

Chiral SFC: retention time: 1.115 min; chromatographic column: Chiralcel AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.64 (m, 1H), 7.48 – 7.26 (m, 2H), 7.07 – 6.96 (m, 1H), 6.82 – 6.67 (m, 1H), 5.98 – 5.57 (m, 1H), 4.37 – 4.28 (m, 1H), 3.69 – 3.33 (m, 8H), 3.16 – 3.00 (m, 2H), 2.62 – 2.55 (m, 3H), 2.41 – 1.66 (m, 14H), 1.52 – 1.32 (m, 2H), 1.31 – 0.80 (m, 12H), 0.30 (d, J = 6.4 Hz, 2H).

Step 4

4-[(4*S*)-4-[3-(8-{2-[(2,2-difluoroethyl)(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **459a-2**

Compound **454d-2** (200.00 mg, 396.74 μmol), Compound **94d**(176.73 mg, 476.09 μmol) and potassium phosphate (252.64 mg, 1.19 mmol) were dissolved in dioxane (5 mL) and water (1 mL). Xphos-Pd-G4 (34.14 mg, 39.67 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **459a-2** (260 mg, 364.72 μmol, yield: 91.93%).

MS m/z (ESI): 713.4 [M+1]

Step 5

N-(2,2-difluoroethyl)-5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-(piperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459b-2**

Compound **459a-2**(130.00 mg, 182.36 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **459b-2** (110 mg, 179.51 μmol, yield: 98.44%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 613.4 [M+1]

Step 6

N-(2,2-difluoroethyl)-5-fluoro-2-(6-{1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **459-2**

The crude product of Compound **459b-2** (110.00 mg, 179.51 μmol) was dissolved in acetonitrile (3.0 mL), followed by the addition of 2-bromoethanol (26.92 mg, 215.42 μmol) and potassium carbonate (74.43 mg, 538.54 μmol), and the mixture was stirred at 80°C for 12 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 34%-54%). The title Compound **459-2** (20.38 mg, 314.03 μmol, yield: 17.28%) was obtained.

Single-configuration Compound 459-2:

MS m/z (ESI):657.5 [M+1]

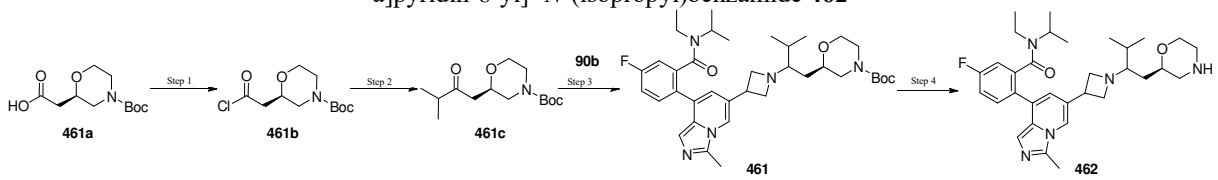
Chiral SFC: retention time: 1.231 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.65 (m, 1H), 7.48 – 7.26 (m, 2H), 7.05 – 6.97 (m, 1H), 6.81 – 6.70 (m, 1H), 5.94 – 5.59 (m, 1H), 4.36 – 4.28 (m, 1H), 3.71 – 3.34 (m, 8H), 3.13 – 3.01 (m, 2H), 2.63 – 2.54 (m, 3H), 2.48 – 1.62 (m, 14H), 1.49 – 1.34 (m, 2H), 1.31 – 0.79 (m, 12H), 0.30 (d, J = 6.4 Hz, 2H).

Example 461,462

(2*R*)-2-{2-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl}morpholin-4-tert-butyl carboxylate **461**

N-ethyl-5-fluoro-2-[3-methyl-6-(1-{3-methyl-1-[(2*R*)-morpholin-2-yl]butan-2-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]- *N*-(isopropyl)benzamide **462**



Step 1

(2*R*)-2-(2-chloro-2-oxyethyl)morpholin-4-tert-butyl carboxylate **461b**

2-[(2*R*)-4-[(tert-butoxy)carbonyl]morpholin-2-yl]acetic acid (1 g, 4.08 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of DMF (14.90 mg, 203.86 μmol). The mixture was cooled to 0°C, followed by the addition of $SOCl_2$ (727.58 mg, 6.12 mmol). The reaction mixture was stirred at room temperature for 1.0 hour, and concentrated under a reduced pressure, to obtain the crude product of title Compound **461b** (1 g, 3.79 mmol, yield: 93.01%). The crude product was directly used in the next step of reaction.

Step 2

(2*R*)-2-(3-methyl-2-oxobutyl)morpholin-4-tert-butyl carboxylate **461c**

Under the protection of nitrogen, Compound **461b**(1.08 g, 4.10 mmol) was dissolved in tetrahydrofuran (15 mL), followed by the addition of ferric acetylacetonate (723.17 mg, 2.05 mmol). Under the protection of nitrogen, the mixture was cooled to 0°C, followed by the slow dropwise addition of an isopropylmagnesium chloride solution (2.0 M, 2.05 mL). After the completion of dropwise addition, the mixture was further stirred at 0°C for 1.0 hours. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution (20 mL), and extracted with ethyl acetate (15 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **461c** (120 mg, 442.23 μmol, yield: 10.8%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 – 3.76 (m, 4H), 3.53 (dt, J = 2.5, 11.6 Hz, 1H), 2.98 – 2.82 (m, 1H), 2.78 – 2.55 (m, 3H), 2.44 (dd, J = 4.6, 16.4 Hz, 1H), 1.47 (s, 9H), 1.11 (d, J = 7.0 Hz, 6H).

Step 3

(2*R*)-2-{2-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-3-methylbutyl}morpholin-4-tert-butyl carboxylate **461**

Compound **90b** (180 mg, 456.29 μmol) and Compound **461c**(123.82 mg, 456.29 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (124.38 mg, 912.58 μmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (86.02 mg, 1.37 mmol) and stirring at 50°C for 10 hour. A saturated aqueous sodium bicarbonate solution (5.0 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **461** (150 mg, 230.83 μmol, yield: 50.59%) as white solid.

MS m/z (ESI): 650.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.86 (m, 1H), 7.75 – 7.60 (m, 1H), 7.45 – 7.23 (m, 2H), 7.12 – 6.98 (m, 1H), 6.90 – 6.65 (m, 1H), 3.85 – 3.42 (m, 8H), 3.29 – 2.74 (m, 6H), 2.59 (s, 3H), 2.31 – 2.19 (m, 1H), 1.80 – 1.69 (m, 1H), 1.42 – 1.33 (m, 11H), 0.93 – 0.71 (m, 14H), 0.30 – 0.24 (m, 2H).

Step 4

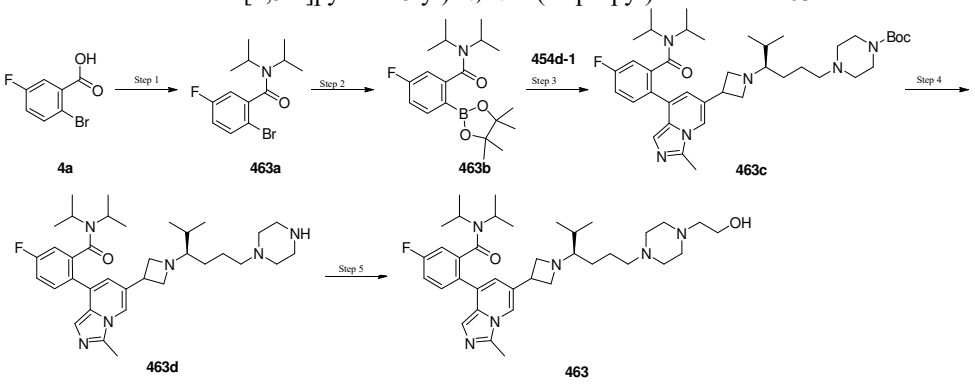
N-ethyl-5-fluoro-2-[3-methyl-6-(1-{3-methyl-1-[(2*R*)-morpholin-2-yl]butan-2-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **462**

Compound **461** (120 mg, 184.66 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL), and the mixture was stirred at 25°C for 1.0 hour. The reaction

mixture was concentrated under a reduced pressure, and purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 29%-59%), to obtain the title Compound **462** (93 mg, 169.18 μmol, yield: 91.64%) as yellow solid.
MS m/z (ESI): 550.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.84 (m, 1H), 7.75 – 7.62 (m, 1H), 7.45 – 7.26 (m, 2H), 7.09 – 6.98 (m, 1H), 6.84 – 6.66 (m, 1H), 4.35 – 3.38 (m, 6H), 3.28 – 2.54 (m, 11H), 2.48 – 2.13 (m, 3H), 1.79 – 1.66 (m, 1H), 1.35 – 0.72 (m, 15H), 0.32 – 0.25 (m, 2H).

Example 463

5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N, N*-di(isopropyl)benzamide **463**



Step 1

2-bromo-5-fluoro- *N,N*-di(isopropyl)benzamide **463a**

N-isopropylprop-2-amine (508.24 mg, 5.02 mmol) and triethylamine (1.39 g, 13.70 mmol) were added to the solution of 2-bromo-5-fluoro-benzoic acid **4a**(1 g, 4.57 mmol) in dichloromethane (10 mL), followed by the slow addition of HATU (2.08 g, 5.48 mmol). The mixture was stirred at 25°C for 12 hours. Water (100 mL) was added to the reaction mixture, which was then extracted with dichloromethane (100 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **463a** (0.46 g, 1.52 mmol, yield33.34%) as yellow solid.
MS m/z (ESI): 303.9 [M+1]

Step 2

5-fluoro-*N,N*-di(isopropyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)benzamide **463b**

Compound **463a** (2 g, 6.62 mmol), potassium acetate (1.95 g, 19.86 mmol) and bis(pinacolato)diboron (3.36 g, 13.24 mmol) were dissolved in DMSO (10 mL). Under a nitrogen atmosphere, Pd(dppf)Cl_2 (242.14 mg, 330.93 μmol) was added, and the mixture was stirred at 110°C to allow for reacting for 12 hours. The mixture was cooled to room temperature, followed by adding 50 mL of ethyl acetate and washing with water (30ml×3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, and the resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **463b** (900 mg, 2.58 mmol, yield: 38.94%) as yellow solid.
MS m/z (ESI): 349.8 [M+1]

Step 3

4-[(4*R*)-4-[3-(8-{2-[di(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-tert-butyl carboxylate **463c**

Compound **454d-1** (220 mg, 436.42 μmol), Compound **463b**(179.31 mg, 349.13 μmol) and potassium phosphate (277.91 mg, 1.31 mmol) were dissolved in dioxane (20 mL) and water (5 mL). Pd(dtbpf)Cl_2 (28.44 mg, 43.64 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (20 mL) and extracting with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **463c** (141 mg, 204.07 μmol, yield: 46.76%) as yellow oil.
MS m/z (ESI): 691.5 [M+1]

Step 4

5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-(piperazin-1-yl)hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **463d**

Compound **463c** (200 mg, 289.46 μmol) was dissolved in dichloromethane (12 mL), followed by the addition of trifluoroacetic acid (4 mL). The mixture was stirred at 25℃ to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH >7 with a 10% aqueous NaOH solution and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **463d** (171 mg, 289.43 μmol, yield: 99.99%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 591.4 [M+1]

Step 5

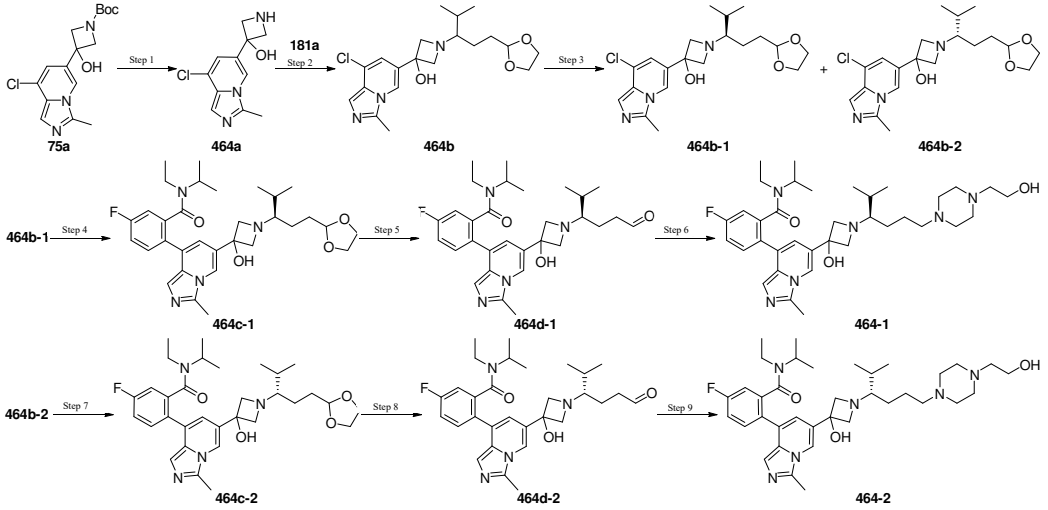
5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methyl-imidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **463**

The crude product of Compound **463d** (170 mg, 287.74 μmol) was dissolved in acetonitrile (10.0 mL), followed by the addition of 2-bromoethanol (39.55 mg, 316.51 μmol) and potassium carbonate (119.30 mg, 863.21 μmol), and the mixture was stirred at 80°C for 2 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 32%-52%). The title Compound **463** (61.28 mg, 96.52 μmol, yield: 33.55%) was obtained as yellow solid.
MS m/z (ESI):635.5 [M+1]
Chiral SFC: retention time: 1.241 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.71 (dd, J = 5.6, 8.8 Hz, 1H), 7.32 (dt, J = 2.4, 8.0 Hz, 1H), 7.18 (dd, J = 2.8, 8.8 Hz, 1H), 7.13 (s, 1H), 6.92 (d, J = 7.0 Hz, 1H), 3.81 – 3.62 (m, 5H), 3.55 – 3.47 (m, 1H), 3.42 – 3.33 (m, 2H), 3.24 (t, J = 7.2 Hz, 1H), 2.66 (s, 3H), 2.63 – 2.42 (m, 8H), 2.36 (q, J = 7.6 Hz, 2H), 2.28 – 2.22 (m, 1H), 1.92 – 1.81 (m, 1H), 1.68 – 1.53 (m, 2H), 1.48 (d, J = 6.8 Hz, 3H), 1.45 – 1.20 (m, 3H), 1.19 – 1.14 (m, 3H), 1.08 – 0.85 (m, 10H), 0.24 (d, J = 6.4 Hz, 3H).

Examples 464-1 and 464-2

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464-1**

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464-2**



Step 1

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-3-ol **464a**

Compound **75a** (1.2 g, 3.55 mmol) was dissolved in dichloromethane (15.0 mL), followed by the addition of trifluoroacetic acid (7.40 g, 64.90 mmol, 5 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (20 mL), regulating to pH > 7 with a 10% aqueous sodium hydroxide solution, and extracting with dichloromethane (40 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **464a** (840 mg, 3.53 mmol, yield: 99.48%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

Step 2

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-ol **464b**

Compound **464a** (840 mg, 3.53 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a**(669.51 mg, 3.89 mmol) were dissolved in methanol (1.82 mL), followed by the addition of acetic acid (212.23 mg, 3.53 mmol), and the mixture was stirred at 40°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (666.27 mg, 10.60 mmol) and stirring at 40°C for 15 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **464b** (1.35 g, 3.43 mmol, yield: 96.98%) as yellow oil.

MS m/z (ESI): 394.0 [M+1]

Step 3

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-ol **464b-1**

3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}-1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-ol **464b-2**

Compound **464b** (1.35 g, 3.43 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-methanol (0.1% ammonia water); elution gradient: 15%), to obtain the title Compounds **464b-1** (600 mg, 1.52 mmol, yield: 44.44%) and **464b-2** (650 mg, 1.65 mmol, yield: 48.15%).

Single-configuration Compound 464b-1:

MS m/z (ESI): 394.2 [M+1]

Chiral HPLC analysis: retention time: 1.166 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 464b-2:

MS m/z (ESI): 394.6 [M+1]

Chiral HPLC analysis: retention time: 1.300 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 4

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]-3-hydroxylazacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **464c-1**

Compound **464b-1** (460.00 mg, 1.17 mmol), Compound **4c**(587.20 mg, 1.75 mmol) and potassium phosphate (743.65 mg, 3.50 mmol) were dissolved in dioxane (5.0 mL) and water (1.0 mL). $Pd(dtbpf)Cl_2$ (76.11 mg, 116.78 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 12 hours. The reaction mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ethyl acetate (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **464c-1** (130 mg, 229.40 μmol, yield: 19.64%) as yellow solid.

MS m/z (ESI): 567.3[M+1]

Step 5

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464d-1**

Compound **464c-1** (130.00 mg, 229.40 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a saturated aqueous potassium carbonate solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **464d-1** (118 mg, 225.77 μmol, yield: 98.42%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 464d-1:

MS m/z (ESI): 523.2 [M+1]

Step 6

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464-1**

The crude product of Compound **464d-1** (118.00 mg, 225.77 μmol) and 2-(piperazin-1-yl)ethanol (35.27 mg, 270.93

μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (13.56 mg, 225.77 μmol). Under the protection of nitrogen, the mixture was stirred at room temperature for 1.0 hour. Sodium cyanoborohydride (42.56 mg, 677.31 μmol) was added, allowing for reacting at room temperature for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%). The title Compound **464-1** (67.33 mg, 105.73 μmol, yield: 46.83%) was obtained as white solid.

Single-configuration Compound 464-1:

MS m/z (ESI):637.3 [M+1]

Chiral SFC: retention time: 1.240 min; chromatographic column: Chiralpak OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 7.91 (m, 1H), 7.71 – 7.58 (m, 1H), 7.43 – 7.22 (m, 2H), 7.13 – 6.92 (m, 2H), 5.99 (s, 1H), 4.40 – 4.21 (m, 1H), 3.67 – 3.53 (m, 1H), 3.52 – 3.39 (m, 4H), 3.30 – 2.64 (m, 5H), 2.59 (s, 3H), 2.41 – 2.16 (m, 11H), 2.09 (d, J = 2.4 Hz, 1H), 1.78 – 1.64 (m, 1H), 1.51 – 1.37 (m, 2H), 1.34 – 1.14 (m, 2H), 1.08 – 0.72 (m, 13H), 0.31 (d, J = 6.4 Hz, 2H).

Step 7

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]-3-hydroxylazacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **464c-2**

Compound **464b-2** (550.00 mg, 1.40 mmol), Compound **4c**(936.12 mg, 2.09 mmol) and potassium phosphate (889.14 mg, 4.19 mmol) were dissolved in dioxane (8.0 mL) and water (2.0 mL). Xphos-Pd-G4 (60.07 mg, 69.81 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **464c-2** (600 mg, 1.06 mmol, yield: 75.83%) as yellow solid.

MS m/z (ESI): 567.3[M+1]

Step 8

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464d-2**

Compound **464c-2** (120.00 mg, 211.75 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50℃ to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10% aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **464d-2** (110 mg, 210.46 μmol, yield: 99.39%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 464d-2:

MS m/z (ESI): 523.2 [M+1]

Step 9

N-ethyl-5-fluoro-2-(6-{3-hydroxyl-1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **464-2**

The crude product of Compound **464d-2** (110 mg, 210.46 μmol) and 2-(piperazin-1-yl)ethanol (32.88 mg, 252.56 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (12.64 mg, 210.46 μmol). Under the protection of nitrogen, the mixture was stirred at 50℃ for 0.5 hours. Sodium cyanoborohydride (39.68 mg, 631.39 μmol) was added, allowing for reacting at 50℃ for 1.5 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 20%-50%). The title Compound **464-2** (33.30 mg, 52.29 μmol, yield: 24.84%) was obtained as white solid.

Single-configuration Compound 464-2:

MS m/z (ESI):637.2 [M+1]

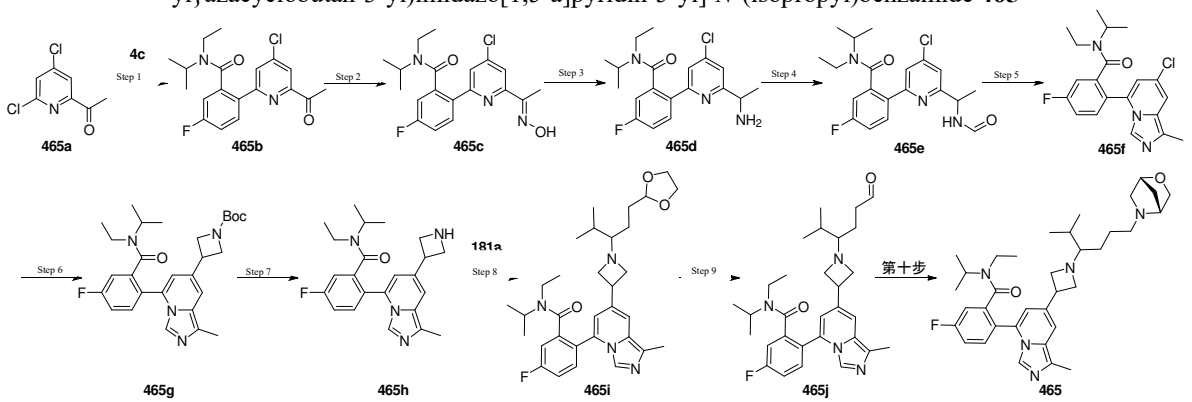
Chiral SFC: retention time: 1.255 min; chromatographic column: Chiralpak OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.95 (m, 1H), 7.75 – 7.56 (m, 1H), 7.43 – 7.21 (m, 2H), 7.13 – 6.94 (m,

2H), 6.20 – 5.57 (m, 1H), 4.37 – 4.22 (m, 1H), 3.66 – 3.56 (m, 1H), 3.52 – 3.40 (m, 4H), 3.31 – 2.73 (m, 5H), 2.61 – 2.57 (m, 3H), 2.40 – 2.16 (m, 11H), 2.12 – 2.05 (m, 1H), 1.77 – 1.66 (m, 1H), 1.48 – 1.37 (m, 2H), 1.31 – 1.17 (m, 2H), 1.04 – 0.73 (m, 13H), 0.33 – 0.29 (m, 2H).

Example 465

N-ethyl-5-fluoro-2-[1-methyl-7-(1-{2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]hexan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-5-yl]-*N*-(isopropyl)benzamide **465**



Step 1

2-(6-acetyl-4-chloropyridin-2-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465b**

1-(4,6-Dichloropyridin-2-yl)ethan-1-one **465a** (1 g, 5.26 mmol), Compound **4c**(1.76 g, 5.26 mmol) and sodium carbonate (1.67 g, 15.79 mmol) were dissolved in dioxane (10 mL) and water (2.0 mL). Under a nitrogen atmosphere, $Pd(dppf)Cl_2$ (385.05 mg, 526.24 μmol) was added, and the mixture was stirred at 70°C to allow for reacting for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding water (250 mL) and extracting with ethyl acetate (100 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **465b** (1.5 g, 4.13 mmol, yield: 78.56%).

MS m/z (ESI): 276.0 [M+1]

^1H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.96 (m, 1H), 7.86 – 7.78 (m, 2H), 7.27 – 7.19 (m, 1H), 7.16 – 7.08 (m, 1H), 3.55 (qd, J = 6.7, 13.4 Hz, 2H), 3.07 (dd, J = 6.9, 13.7 Hz, 1H), 2.77 – 2.73 (m, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.05 – 0.82 (m, 4H), 0.49 (d, J = 6.6 Hz, 2H)**.**

Step 2

2-{4-chloro-6-[1-(hydroxylimino)ethyl]pyridin-2-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465c**

Compound **465b** (500 mg, 1.38 mmol) and hydroxylamine (105.34 mg, 1.52 mmol, hydrochloride) were dissolved in methanol (10 mL). Under a nitrogen atmosphere, potassium carbonate (571.37 mg, 4.13 mmol) was added, and the mixture was stirred at 25°C to allow for reacting for 4.0 hours. The reaction mixture was filtered and washed with methanol, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **465c**. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 378.1 [M+1]

Step 3

2-[6-(1-aminoethyl)-4-chloropyridin-2-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465d**

Compound **465c** (520 mg, 1.38 mmol) was dissolved in methanol (10 mL). Ammonium chloride (368.09 mg, 6.88 mmol) was added to the reaction mixture, and under a nitrogen atmosphere, zinc powder (449.96 mg, 6.88 mmol) was added. The mixture was stirred at room temperature to allow for reacting for 4 hour. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the crude product of title Compound **465d** (677 mg, 1.86 mmol, yield: 135.2%). The crude product was directly used in the next step of reaction without further purification.

MS m/z (ESI): 363.9 [M+1]

Step 4

2-[4-chloro-6-(1-formamide ethyl)pyridin-2-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465e**

Compound **465d** (677 mg, 1.86 mmol) was dissolved in ethyl formate (6.20 g, 83.73 mmol, 6.73 mL), followed by the addition of triethylamine (564.82 mg, 5.58 mmol) under a nitrogen atmosphere. The mixture was stirred at 60°C to allow for reacting for 12 hours, and the reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution

system, to obtain the title Compound **465e** (447 mg, 1.14 mmol, yield: 61.31%) as white solid.
MS m/z (ESI): 391.9 [M+1]

Step 5

2-{7-chloro-1-methylimidazo[1,5-a]pyridin-5-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465f**

Compound **465e** (447 mg, 1.14 mmol) was dissolved in toluene (10 mL). $POCl_3$ (874.53 mg, 5.70 mmol) was added, and the mixture was stirred at 100°C to allow for reacting for 1.0 hour. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The residues were diluted with dichloromethane (20 mL), and slowly dropwise added to a saturated aqueous sodium bicarbonate solution (20 mL), and the mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **465f** (360 mg, 962.95 μmol, yield: 84.42%) as yellow solid.
MS m/z (ESI): 374.0 [M+1]

Step 6

3-(5-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-1-methylimidazo[1,5-a]pyridin-7-yl)azacyclobutan-1-tert-butyl carboxylate **465g**

Compound **465f** (1 g, 2.67 mmol) was dissolved in DMF(20 mL), followed by the addition of $Pd_2(dba)_3$ (153.81 mg, 267.49 μmol) and RuPhos (124.82 mg, 267.49 μmol). Under a nitrogen atmosphere, {1-[(tert-butoxy)carbonyl]azacyclobutan-3-yl}zinc iodide (932.18 mg, 2.67 mmol) was added. The mixture was stirred at 100°C to allow for reacting for 12 hours. The reaction mixture was cooled to room temperature under a reduced pressure, added to 100 mL of water, and extracted with ethyl acetate (20 mL x 3), and the organic phases were combined, washed with a 5% aqueous lithium chloride solution (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **465g** (560 mg, 1.13 mmol, yield: 42.33%).
MS m/z (ESI): 495.1 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.71 (m, 2H), 7.50 – 7.39 (m, 3H), 6.48 – 6.38 (m, 1H), 4.25 – 4.12 (m, 2H), 3.85 (br s, 2H), 3.78 – 3.68 (m, 1H), 3.62 – 3.45 (m, 1H), 2.97 – 2.84 (m, 1H), 2.54 (s, 2H), 2.41 (s, 3H), 1.39 (s, 9H), 1.02 – 0.88 (m, 4H), 0.87 – 0.63 (m, 4H).

Step 7

2-[7-(azacyclobutan-3-yl)-1-methylimidazo[1,5-a]pyridin-5-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465h**

Compound **465g** (500 mg, 1.01 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of 2,6-dimethylpyridine (433.29 mg, 4.04 mmol), cooling to 0°C, and the slow dropwise addition of TMSOTf (674.05 mg, 3.03 mmol), and the mixture was stirred at 0°C to allow for reacting for 2 hours. At 0°C, a saturated aqueous ammonium chloride solution (20 mL) was added dropwise to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the title Compound **465h** (398 mg, 1.01 mmol, yield: 99.8%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 395.1 [M+1]

Step 8

2-(7-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-1-methylimidazo[1,5-a]pyridin-5-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **465i**

Compound **465h** (398 mg, 1.01 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (173.76 mg, 1.01 mmol) were dissolved in methanol (10 mL), followed by the addition of $ZnCl_2$(275.02 mg, 2.02 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (190.21 mg, 3.03 mmol) and stirring at 50°C for 11 hour. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **465i** (44 mg, 79.90 μmol, yield: 7.92%).
MS m/z (ESI): 551.2 [M+1]

Step 9

N-ethyl-5-fluoro-2-{1-methyl-7-[1-(2-methyl-6-oxohexan-3-yl)azacyclobutan-3-yl]imidazo[1,5-a]pyridin-5-yl}-*N*-(isopropyl)benzamide **465j**

Compound **465i** (30 mg, 54.48 μmol) was dissolved in acetonitrile (3.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH

solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **465j** (36 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 507.2 [M+1]

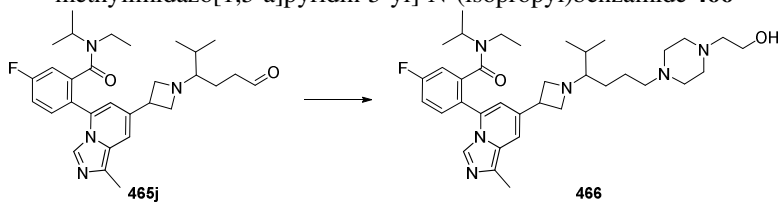
Step 10

N-ethyl-5-fluoro-2-[1-methyl-7-(1-{2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]hexan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-5-yl]-*N*-(isopropyl)benzamide **465**

(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (49.46 mg, 364.75 μmol, hydrochloride) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (100.66 mg, 994.76 μmol), and then the addition of Compound **465j** (110 mg, 204.22 μmol). Under the protection of nitrogen, the mixture was stirred at 35℃ for 1.0 hours. Sodium cyanoborohydride (210.83 mg, 994.76 μmol) was added, allowing for reacting at 35℃ for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **465** (59.41 mg, 100.73 μmol, yield: 30.38%) as yellow solid.
MS m/z (ESI): 590.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.74 – 7.56 (m, 1H), 7.26 – 7.06 (m, 3H), 6.67 – 6.39 (m, 1H), 4.47 – 4.27 (m, 1H), 4.03 (br d, J = 7.8 Hz, 1H), 3.84 – 3.36 (m, 7H), 3.23 – 3.04 (m, 2H), 2.97 – 2.79 (m, 2H), 2.64 – 2.54 (m, 1H), 2.52 (s, 3H), 2.49 (br s, 1H), 2.14 – 2.02 (m, 1H), 1.98 – 1.69 (m, 5H), 1.51 (br s, 2H), 1.39 – 1.25 (m, 2H), 1.06 – 0.74 (m, 12H), 0.28 – 0.01 (m, 2H).

Example 466

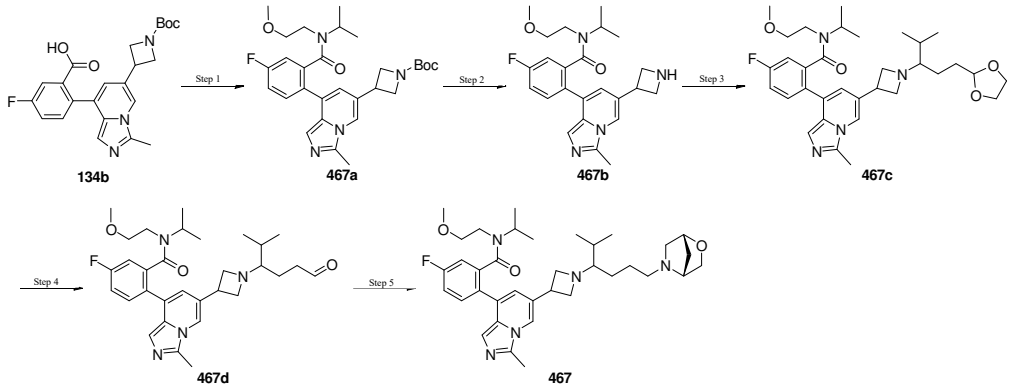
N-ethyl-5-fluoro-2-[7-(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)-1-methylimidazo[1,5-a]pyridin-5-yl]-N-(isopropyl)benzamide **466**



Compound **465j** (36 mg, 71.05 μmol) was dissolved in methanol (2.0 mL), followed by the addition of 2-(piperazin-1-yl)ethanol (10.18 mg, 78.16 μmol) and acetic acid (426.70 μg, 7.11 μmol). Under the protection of nitrogen, the mixture was stirred at 35℃ for 1.0 hours. Sodium cyanoborohydride (13.40 mg, 213.16 μmol) was added, allowing for reacting at 35℃ for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 23%-53%), to obtain the title Compound **466** (12.53 mg, 20.18 μmol, yield: 28.40%) as yellow solid.
MS m/z (ESI): 621.3 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.73 – 7.63 (m, 1H), 7.26 – 7.10 (m, 3H), 6.65 – 6.46 (m, 1H), 3.83 – 3.42 (m, 7H), 3.21 – 3.05 (m, 2H), 2.96 – 2.81 (m, 1H), 2.66 – 2.53 (m, 6H), 2.52 (s, 3H), 2.50 – 2.44 (m, 2H), 2.33 (br t, J = 7.6 Hz, 2H), 2.17 – 2.01 (m, 1H), 1.87 – 1.75 (m, 2H), 1.56 (br d, J = 4.0 Hz, 3H), 1.39 – 1.24 (m, 2H), 1.15 – 0.72 (m, 13H), 0.28 – 0.02 (m, 2H).

Example 467

5-fluoro-*N*-(2-methoxyethyl)-2-[3-methyl-6-(1-{2-methyl-6-(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl}hexan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **467**



Step 1

3-(8-{4-fluoro-2-[(2-methoxyethyl)(isopropyl)aminoformyl]phenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **467a**

Compound **134b** (250 mg, 587.61 μmol) was dissolved in dichloromethane (4 mL), followed by the addition of DIPEA (151.89 mg, 1.18 mmol) and HATU (268.11 mg, 705.13 μmol), respectively, and finally the addition of *N*-(2-methoxyethyl)prop-2-amine (103.29 mg, 881.42 μmol). Under a nitrogen atmosphere, the mixture was stirred at 25°C to allow for reacting for 2.0 hours. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **467a** (300 mg, 571.84 μmol, yield: 97.32%) as yellow solid.

MS m/z (ESI): 525.3 [M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-fluoro-*N*-(2-methoxyethyl)- *N*-(isopropyl)benzamide **467b**

Compound **467a** (250 mg, 476.53 μmol) was dissolved in dichloromethane (3 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL), and the mixture was stirred at 25°C to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, the resulting crude product was dissolved with dichloromethane (2 mL) and regulated to PH = 10 with a 1N aqueous NaOH solution, and the mixture was extracted with dichloromethane (20 mL x 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the title Compound **467b** (200 mg, 471.13 μmol, yield: 98.87%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 425.0 [M+1]

Step 3

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N*-(2-methoxyethyl)-*N*-(isopropyl)benzamide **467c**

Compound **467b** (200 mg, 471.13 μmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (97.37 mg, 565.36 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (28.29 mg, 471.13 μmol), and the mixture was stirred at 40°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (88.82 mg, 1.41 mmol) and stirring at 40°C for 12 hour. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **467c** (150 mg, 258.29 μmol, yield: 54.82%).

MS m/z (ESI): 581.4 [M+1]

Step 4

5-fluoro-*N*-(2-methoxyethyl)-2-{3-methyl-6-[1-(2-methyl-6-oxohexan-3-yl)azacyclobutan-3-yl]imidazo[1,5-a]pyridin-8-yl}-*N*-(isopropyl)benzamide **467d**

Compound **467c** (100 mg, 172.20 μmol) was dissolved in acetonitrile (1.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **467d** (90

mg, 167.70 μmol, yield: 97.39%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 537.3 [M+1]

Step 5

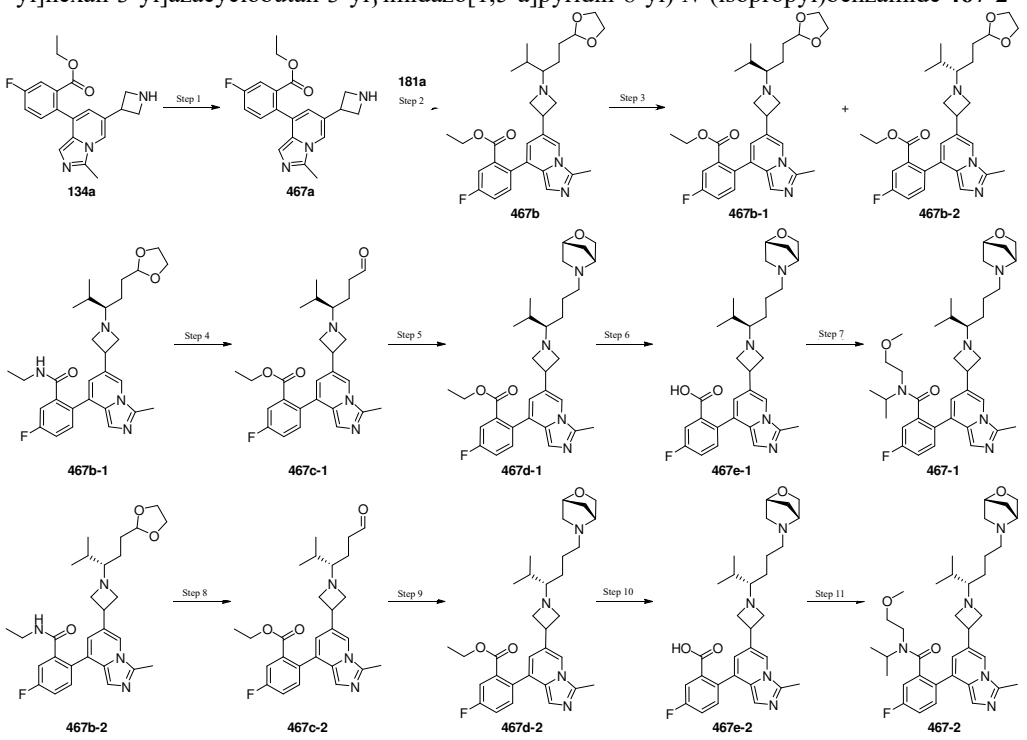
5-fluoro-*N*-(2-methoxyethyl)-2-[3-methyl-6-(1-{2-methyl-6-(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl}hexan-3-yl}azacyclobutan-3-yl)imidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **467**

(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (27.29 mg, 201.24 μmol, hydrochloride) was dissolved in methanol (2.0 mL), followed by the addition of triethylamine (33.94 mg, 335.40 μmol) and then the addition of Compound **467d** (90 mg, 167.70 μmol). Under the protection of nitrogen, the mixture was stirred at 40℃ for 0.5 hours. Sodium cyanoborohydride (31.62 mg, 503.09 μmol) was added, allowing for reacting at 40℃ for 1.5 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% formic acid), elution gradient: 10%), to obtain the title Compound **467** (5.15 mg, 8.31 μmol, yield: 4.95%) as yellow solid.
MS m/z (ESI): 620.4 [M+1]
^{1}H NMR (400 MHz,DMSO-d_6) δ 8.02 – 7.84 (m, 1H), 7.74 – 7.57 (m, 1H), 7.46 – 7.26 (m, 2H), 7.08 – 6.92 (m, 1H), 6.90 – 6.67 (m, 1H), 4.31 – 4.10 (m, 1H), 3.84 – 3.72 (m, 1H), 3.62 – 3.35 (m, 7H), 3.18 – 2.96 (m, 7H), 2.89 – 2.79 (m, 1H), 2.75 – 2.66 (m, 1H), 2.61 – 2.56 (m, 3H), 2.48 – 2.28 (m, 3H), 2.07 – 1.99 (m, 1H), 1.78 – 1.63 (m, 2H), 1.56 – 1.48 (m, 1H), 1.45 – 1.33 (m, 2H), 1.32 – 1.17 (m, 2H), 1.07 – 0.79 (m, 10H), 0.32 – 0.25 (m, 2H).

Examples 467-1 and 467-2

5-fluoro-*N*-(2-methoxyethyl)-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **467-1**

5-fluoro-*N*-(2-methoxyethyl)-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **467-2**



Step 1

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-5-ethyl fluorobenzoate **467a**

Compound **134a** (2.5 g, 5.51 mmol) was dissolved in methane dioxide (15.0 mL), followed by the addition of trifluoroacetic acid (7.40 g, 64.90 mmol, 5 mL). The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, and the resulting crude product was regulated to PH = 10 with a 1M aqueous sodium hydroxide solution and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **467a** (1.9 g, 5.38 mmol, yield: 97.53%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 354.2 [M+1]

Step 2

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-ethyl fluorobenzoate **467b**

Compound **467a** (1.9 g, 5.38 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (1.11 g, 6.45 mmol) were dissolved in methanol (20.0 mL), followed by the addition of acetic acid (322.87 mg, 5.38 mmol), and the mixture was stirred at 40°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (1.01 g, 16.13 mmol) and stirring at 40°C for 12 hour. A saturated aqueous sodium bicarbonate solution (25 mL) was added to the reaction mixture, which was then extracted with dichloromethane (25 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **467b** (2 g, 3.92 mmol, yield: 72.99%)

MS m/z (ESI): 510.2 [M+1]

Step 3

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-ethyl fluorobenzoate **467b-1**

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-ethyl fluorobenzoate **467b-2**

Compound **467b** (2 g, 3.92 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 30%), to obtain the title Compounds **467b-1** (800 mg, 1.57 mmol, yield: 40%) and **467b-2** (850 mg, 1.67 mmol, yield: 42.5%).

Single-configuration Compound 467b-1:

MS m/z (ESI):510.2 [M+1]

Chiral HPLC analysis: retention time: 1.452 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 467b-2:

MS m/z (ESI):510.3 [M+1]

Chiral HPLC analysis: retention time: 1.597 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 4

5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)ethyl benzoate **467c-1**

Compound **467b-1** (600.00 mg, 1.18 mmol) was dissolved in acetonitrile (6.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 6.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH = 10 with a10 % aqueous NaOH solution, and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **467c-1** (540 mg, 1.16 mmol,yield: 98.52%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 467c-1:

MS m/z (ESI): 466.3 [M+1]

Step 5

5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)ethyl benzoate **467d-1**

The crude product of Compound **467c-1** (540 mg, 1.16 mmol) and (1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptane (188.73 mg, 1.39 mmol, hydrochloride) were dissolved in methanol (10.0 mL), followed by the addition of triethylamine (234.74 mg, 2.32 mmol), and the mixture was stirred at 40°C for 0.5 hours. Sodium cyanoborohydride (737.49 mg, 3.48 mmol) was added, allowing for reacting 40°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **467d-1** (500 mg, 911.26 μmol, yield: 78.56%) as yellow solid.

Single-configuration Compound 467d-1:

MS m/z (ESI):549.3 [M+1]

Step 6

5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoic acid **467e-1**

Compound **467d-1** (70 mg, 127.58 μmol) was dissolved in acetonitrile (1.0 mL), followed by the addition of potassium trimethylsilanolate (24.55 mg, 191.36 μmol). The mixture was stirred at 50℃ to allow for reacting for 14 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **467e-1** (65 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 467e-1:

MS m/z (ESI): 521.4 [M+1]

Step 7

5-fluoro-*N*-(2-methoxyethyl)-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **467-1**

The crude product of Compound **467e-1** (65.00 mg, 124.85 μmol) was dissolved in dichloromethane (1.0 mL), followed by the addition of triethylamine (25.27 mg, 249.69 μmol) and HATU(56.96 mg, 149.82 μmol), and the mixture was stirred at room temperature for 5.0 min. *N*- (2-methoxyethyl)prop-2-amine (17.56 mg, 149.82 μmol) was added, allowing for reacting at 25°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 29%-59%). The title Compound **467-1** (10.94 mg, 17.65 μmol, yield: 14.14%) was obtained as yellow solid.

Single-configuration Compound 467-1:

MS m/z (ESI):620.2 [M+1]

Chiral SFC: retention time: 1.156 min; chromatographic column: Chiralcel OD 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.82 (m, 1H), 7.74 – 7.54 (m, 1H), 7.48 – 7.22 (m, 2H), 7.14 – 6.87 (m, 1H), 6.85 – 6.68 (m, 1H), 4.33 – 4.17 (m, 1H), 3.81 – 3.73 (m, 1H), 3.59 – 3.38 (m, 7H), 3.16 – 2.97 (m, 7H), 2.91 – 2.79 (m, 1H), 2.75 – 2.69 (m, 1H), 2.62 – 2.55 (m, 3H), 2.48 – 2.27 (m, 3H), 2.08 – 1.98 (m, 1H), 1.75 – 1.63 (m, 2H), 1.54 – 1.48 (m, 1H), 1.45 – 1.34 (m, 2H), 1.31 – 1.17 (m, 2H), 1.04 – 0.79 (m, 10H), 0.31 – 0.26 (m, 2H).

Step 8

5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)ethyl benzoate **467c-2**

Compound **467b-2** (600.00 mg, 1.18 mmol) was dissolved in acetonitrile (6.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 6.0 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH = 10 with a10 % aqueous NaOH solution, and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **467c-2** (540 mg, 1.16 mmol,yield: 98.52%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 467c-2:

MS m/z (ESI): 466.2 [M+1]

Step 9

5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)ethyl benzoate **467d-2**

The crude product of Compound **467c-2** (540 mg, 1.16 mmol) and (1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptane (188.73 mg, 1.39 mmol, hydrochloride) were dissolved in methanol (10.0 mL), followed by the addition of triethylamine (234.74 mg, 2.32 mmol), and the mixture was stirred at 30℃ for 1.0 hours. Sodium cyanoborohydride (737.49 mg, 3.48 mmol) was added, allowing for reacting 30℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **467d-2** (500 mg, 911.26 μmol, yield: 78.56%) as yellow solid.

Single-configuration Compound 467d-2:

MS m/z (ESI):549.4 [M+1]

Step 10

5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)benzoic acid **467e-2**

Compound **467d-2** (100.00 mg, 182.25 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of potassium trimethylsilanolate (35.07 mg, 273.38 μmol). The mixture was stirred at 50℃ to allow for reacting for 12 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **467e-2** (90 mg). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 467e-2:

MS m/z (ESI): 521.4 [M+1]

Step 11

5-fluoro-*N*-(2-methoxyethyl)-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-[(1*R*,4*R*)-2-oxa-5-azadicyclo[2.2.1]heptan-5-yl]hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **467-2**

The crude product of Compound **467e-2** (90.00 mg, 172.87 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of triethylamine (52.48 mg, 518.60 μmol) and HATU(78.87 mg, 207.44 μmol), and the mixture was stirred at room temperature for 5.0 min. *N*- (2-methoxyethyl)prop-2-amine (24.31 mg, 207.44 μmol) was added, allowing for reacting at 35℃ for 12.0 hours under the protection of nitrogen. The reaction mixture was concentrated under a reduced pressure. The crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-58%). The title Compound **467-2** (41.88 mg, 67.57 μmol, yield: 39.09%) was obtained as yellow solid.

Single-configuration Compound 467-2:

MS m/z (ESI):620.3 [M+1]

Chiral SFC: retention time: 1.161 min; chromatographic column: Chiralcel OD 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.89 (m, 1H), 7.71 – 7.61 (m, 1H), 7.45 – 7.28 (m, 2H), 7.05 – 6.98 (m, 1H), 6.86 – 6.68 (m, 1H), 4.28 (s, 1H), 3.84 – 3.75 (m, 1H), 3.62 – 3.35 (m, 7H), 3.18 – 2.97 (m, 7H), 2.90 – 2.78 (m, 1H), 2.73 (d, J = 9.6 Hz, 1H), 2.59 (s, 3H), 2.49 – 2.30 (m, 3H), 2.03 (d, J = 2.0 Hz, 1H), 1.78 – 1.63 (m, 2H), 1.51 (d, J = 9.6 Hz, 1H), 1.45 – 1.33 (m, 2H), 1.32 – 1.17 (m, 2H), 1.05 – 0.81 (m, 10H), 0.29 (d, J = 4.8 Hz, 2H).

Example 469

N-ethyl-5-fluoro-2-[6-(1-{1-[(3*R*)-4-(2-hydroxyethyl)morpholin-3-yl]-4-methylpentan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **469**

Step 1

(3*R*)-3-[3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholine **469a**

Compound **449a** (350.00 mg, 712.74 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (6 mL), and the reaction mixture was regulated to PH = 8 with triethylamine, and concentrated under a reduced pressure, to obtain the crude product of title Compound **469a** (300 mg, 767.36 μmol, yield: 107.66%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 391.1 [M+1]

Step 2

(3*R*)-4-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-3-[3-(3-{8-chloro-3-methylimidazo[1,5-a]pyridin-6-yl}azacyclobutan-1-yl)-4-methylpentyl]morpholine **469b**

Compound **469a** (300.00 mg, 767.36 μmol) and 2-[(tert-butyldimethylsilicyl)oxy]acetaldehyde (267.52 mg, 1.53 mmol) were dissolved in methanol (5.0 mL), and the mixture was stirred at 25°C for 1.0 hour. Sodium cyanoborohydride (245.72 mg, 3.84 mmol) was added, and the mixture was stirred at 25℃ for 2.0 hours. 2-[(Tert-butyldimethylsilicyl)oxy]acetaldehyde (267.52 mg, 1.53 mmol) was supplemented, and the mixture was further stirred at 25°C for 2.0 hours. A saturated aqueous potassium carbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **469b** (281 mg, 511.60 μmol, yield: 66.67%).

MS m/z (ESI): 549.3 [M+1]

Step 3

2-[6-(1-{1-[(3*R*)-4-{2-[(tert-butyldimethylsilyl)oxy]ethyl}morpholin-3-yl]-4-methylpentan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **469c**

Compound **469b** (280 mg, 509.78 μmol), Compound **4c**(256.33 mg, 764.66 μmol) and potassium phosphate (324.62 mg, 1.53 mmol) were dissolved in dioxane (4 mL) and water (1 mL). Xphos Pd G4 (43.86 mg, 50.98 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **469c** (273 mg, 378.08 μmol, yield: 74.17%).
MS m/z (ESI): 722.5 [M+1]

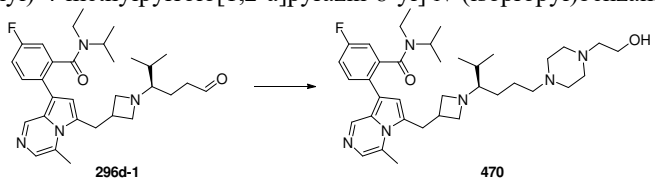
Step 4

N-ethyl-5-fluoro-2-[6-(1-{1-[(3*R*)-4-(2-hydroxyethyl)morpholin-3-yl]-4-methylpentan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyridin-8-yl]-*N*-(isopropyl)benzamide **469**

Compound **469c** (260.00 mg, 360.08 μmol) was dissolved in dichloromethane (0.5 mL), followed by the addition of trifluoroacetic acid (4 mL). The mixture was stirred at room temperature to allow for reacting for 1.0 hour. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL), regulating to PH =8 with triethylamine, and concentrating under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1%ammonium bicarbonate), elution gradient: 28%-58%) two times, to obtain the title Compound **469** (76.1 mg, 125.21 μmol) as yellow solid.
MS m/z (ESI): 608.3 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1 H), 7.64 – 7.73 (m, 1 H), 7.28 – 7.42 (m, 2 H), 7.00 – 7.07 (m, 1 H), 6.75 (br d, J=12.40 Hz, 1 H), 4.32 – 4.44 (m, 1 H), 3.48 – 3.65 (m, 5 H), 3.41 – 3.48 (m, 4 H), 3.21 – 3.32 (m, 2 H), 3.10 – 3.17 (m, 1 H), 3.06 (br t, J=6.00 Hz, 1 H), 2.86 – 2.99 (m, 1 H), 2.66 – 2.75 (m, 2 H), 2.59 (s, 3 H), 2.19 – 2.31 (m, 3 H), 1.99 (br s, 1 H), 1.66 – 1.77 (m, 1 H), 1.34 – 1.57 (m, 2 H), 1.33 (br s, 3 H), 0.86 – 0.93 (m, 4 H), 0.81 – 0.85 (m, 5 H), 0.76 – 0.80 (m, 2 H), 0.73 (br t, J=7.20 Hz, 1 H), 0.28 (br d, J=6.40 Hz, 2 H).

Example 470

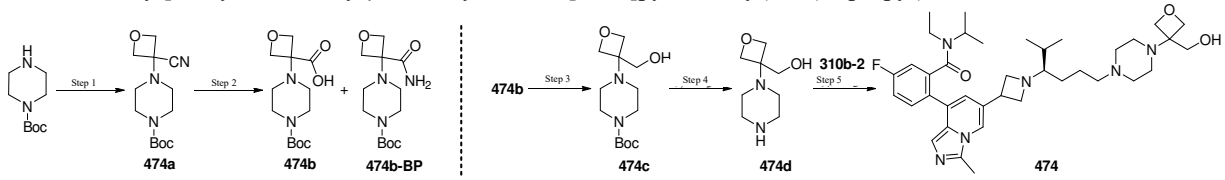
N-ethyl-5-fluoro-2-[6-({1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **470**



Compound **296d-1** (90 mg, 172.85 μmol) and 2-(piperazin-1-yl)ethanol (45.01 mg, 345.70 μmol) were dissolved in methanol (2 mL), followed by the addition of acetic acid (15.57 mg, 259.28 μmol), and the mixture was stirred at room temperature for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (27.16 mg, 432.13 μmol) was added, allowing for reacting at room temperature for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, and the obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonium bicarbonate), elution gradient: 28%-58%). The title Compound **470** (46.51 mg, 73.26 μmol, yield: 42.38%) was obtained.
MS m/z (ESI):635.4 [M+1]
Chiral SFC: retention time: 1.374 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.57 – 7.49 (m, 1H), 7.36 – 7.17 (m, 3H), 6.65 – 6.56 (m, 1H), 4.36 – 4.28 (m, 1H), 3.55 – 3.34 (m, 7H), 3.26 – 2.95 (m, 2H), 2.83 – 2.74 (m, 5H), 2.69 – 2.60 (m, 1H), 2.41 – 2.24 (m, 9H), 2.22 – 2.14 (m, 2H), 1.97 – 1.91 (m, 1H), 1.74 – 1.61 (m, 1H), 1.44 – 1.32 (m, 2H), 1.28 – 1.04 (m, 3H), 0.95 – 0.68 (m, 13H), 0.31 – 0.20 (m, 2H).

Example 474

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-{4-[3-(hydroxymethyl)oxacyclobutan-3-yl]piperazin-1-yl}-2-methylhexan-3-yl]azacyclobutan-3yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **474**



Step 1

4-(3-cyanooxacyclobutan-3-yl)piperazin-1-tert-butyl carboxylate **474a**

Piperazin-1-tert-butyl carboxylate (3 g, 16.11 mmol) was dissolved in dichloroethane (40 mL), followed by the addition of oxacyclobutan-3-one (1.74 g, 24.16 mmol) and acetic acid (1.16 g, 19.33 mmol). The reaction mixture was stirred at 50°C for 1.0 hour, followed by the slow dropwise addition of TMSCN (3.08 g, 31.05 mmol). The reaction mixture was stirred at 25℃ for 12 hours. The reaction mixture was quenched by adding a saturated aqueous sodium bicarbonate solution (30 mL), and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **474a** (2.4 g, 8.98 mmol, yield: 55.74%).

MS m/z (ESI): 212.3 [M-56]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, J = 6.4 Hz, 2H), 4.67 (d, J = 6.4 Hz, 2H), 3.53 (br s, 4H), 2.38 (br t, J = 4.7 Hz, 4H), 1.47 (s, 9H).

Step 2

3-{4-[(tert-butoxy)carbonyl]piperazin-1-yl}oxacyclobutan-3-carboxylic acid **474b**

4-(3-aminoformyloxacyclobutan-3-yl)piperazin-1-tert-butyl carboxylate **474b-BP**

Compound **474a** (1.5 g, 5.61 mmol) was dissolved in methanol (10.0 mL), followed by the dropwise addition of aqueous sodium hydroxide solution (2.0 M, 14.03 mL) under the protection of nitrogen. After the completion of dropwise addition, the mixture was stirred at 50℃ for 12 hours. The reaction mixture was concentrated under a reduced pressure to remove methanol, diluted with water (10 mL) diluted, regulated to the PH value of 2-3 with 1M HCl, and then extracted with dichloromethane (15 mL×3), and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **474b-BP** (950 mg, 3.33 mmol, yield: 59.33%). After extraction, the aqueous phase was regulated to the PH value of 4-5, and further extracted with dichloromethane (15 mL×3), and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure, to obtain the title Compound **474b** (210 mg, 733.44 μmol, yield: 13.07%).

Compound **474b-BP:**

MS m/z (ESI): 286.2 [M+1]

Compound **474b:**

MS m/z (ESI): 231.1 [M-56]

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.94 – 12.04 (m, 1H), 4.59 (d, J = 6.4 Hz, 2H), 4.44 (d, J = 6.4 Hz, 2H), 3.36 – 3.34 (m, 5H), 2.38 (br t, J = 4.8 Hz, 4H), 1.39 (s, 9H).

Step 3

4-[3-(hydroxymethyl)oxacyclobutan-3-yl]piperazin-1-tert-butyl carboxylate **474c**

Compound **474b** (210 mg, 733.44 μmol) was dissolved in tetrahydrofuran (5.0 mL), and cooled to 0°C, followed by the slow dropwise addition of an $LiAlH_4$ solution (2.5 M, 440.06 μL), and the mixture was stirred at for 1.0 hour at 0°C. Under the protection of nitrogen, the reaction mixture was quenched by adding sodium sulfate decahydrate, diluted with ethyl acetate and then filtered. The filtrate was concentrated under a reduced pressure, to obtain the title Compound **474c** (100 mg, 367.19 μmol, yield: 50.06%) as colorless oil. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 273.2 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 – 4.08 (m, 6H), 3.96 (br s, 1H), 3.51 – 3.39 (m, 4H), 2.51 (br dd, J = 3.8, 8.8 Hz, 4H), 1.47 (s, 9H).

Step 4

[3-(piperazin-1-yl)oxacyclobutan-3-yl]methanol **474d**

Compound **474c** (100 mg, 367.19 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (0.5 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **474d** (100 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 173.2 [M+1]

Step 5

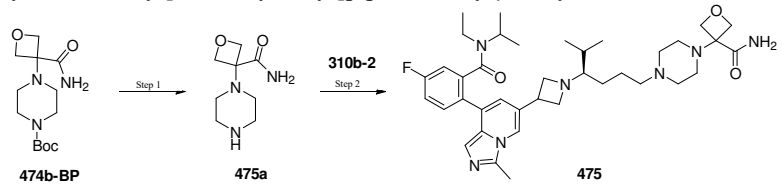
N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-{4-[3-(hydroxymethyl)oxacyclobutan-3-yl]piperazin-1-yl}-2-methylhexan-3-yl]azacyclobutan-3yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **474**

Compound **310b-2** (120 mg, 236.85 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (47.93 mg, 473.70 μmol) and the crude product of Compound **474d** (100 mg). Under the protection of nitrogen, the mixture was stirred at 25℃ for 0.5 hours. Sodium cyanoborohydride (125.49 mg, 592.12 μmol) was added, allowing for reacting at 25℃ for 12 hours under the protection of nitrogen. A saturated aqueous sodium

bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-48%), to obtain the title Compound **474** (55.49 mg, 83.71 μmol, yield: 35.34%) as white solid.
MS m/z (ESI): 663.4 [M+1]
^{1}H NMR (400 MHz,DMSO-d_6) δ 7.92 (s, 1H), 7.73 – 7.63 (m, 1H), 7.43 – 7.27 (m, 2H), 7.07 – 6.99 (m, 1H), 6.88 – 6.71 (m, 1H), 4.84 – 4.79 (m, 1H), 4.31 – 4.24 (m, 4H), 3.72 – 3.65 (m, 2H), 3.60 – 3.40 (m, 4H), 3.31 – 2.87 (m, 4H), 2.59 (s, 3H), 2.49 – 2.18 (m, 10H), 2.05 – 1.99 (m, 1H), 1.77 – 1.65 (m, 1H), 1.51 – 1.37 (m, 2H), 1.30 – 0.96 (m, 3H), 0.91 – 0.71 (m, 12H), 0.29 – 0.25 (m, 2H).

Example 475

3-{4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-yl}oxacyclobutan-3-formamide **475**



Step 1

3-(piperazin-1-yl) oxacyclobutan-3-formamide **475a**

Compound **474b-BP** (110 mg, 385.51 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (0.5 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **475a** (100 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 186.2 [M+1]

Step 2

3-{4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-yl}oxacyclobutan-3-formamide **475**

Compound **310b-2** (120 mg, 236.85 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (47.93 mg, 473.70 μmol) and the crude product of Compound **475a** (100 mg). Under the protection of nitrogen, the mixture was stirred at 25℃ for 0.5 hours. Sodium cyanoborohydride (125.49 mg, 592.12 μmol) was added, allowing for reacting at 25℃ for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 28%-48%), to obtain the title Compound **475** (66.25 mg, 98.02 μmol, yield: 41.39%) as white solid.
MS m/z (ESI): 676.4 [M+1]
^{1}H NMR (400 MHz,DMSO-d_6) δ 7.92 (s, 1H), 7.73 – 7.63 (m, 1H), 7.42 – 7.20 (m, 4H), 7.07 – 7.00 (m, 1H), 6.87 – 6.71 (m, 1H), 4.55 (d, J = 6.8 Hz, 2H), 4.42 (d, J = 6.8 Hz, 2H), 3.62 – 3.40 (m, 4H), 3.32 – 2.88 (m, 4H), 2.59 (s, 3H), 2.47 – 2.16 (m, 10H), 2.05 – 2.00 (m, 1H), 1.76 – 1.66 (m, 1H), 1.51 – 1.38 (m, 2H), 1.30 – 0.96 (m, 3H), 0.91 – 0.71 (m, 12H), 0.29 – 0.26 (m, 2H).

Example 476

3-{4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-yl}-*N,N*-dimethyloxacyclobutan-3-formamide **476**

Step 1

4-[3-(dimethylaminoformyl)oxacyclobutan-3-yl]piperazin-1-tert-butyl carboxylate **476a**

Compound **474b** (160 mg, 558.81 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of *N*-methylmethylamine (68.35 mg, 838.21 μmol, hydrochloride), triethylamine (169.64 mg, 1.68 mmol) and a T4P condensing agent (671.05 mg, 838.21 μmol, 45% purity), and the mixture was stirred at 25°C for 2.0 hours. The reaction mixture was quenched by adding water (10 mL) and extracted with dichloromethane (10 mL×3), and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under a reduced

pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **476a** (100 mg, 319.09 μmol, yield: 57.1%) as colorless oil.
MS m/z (ESI): 314.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, J = 7.6 Hz, 2H), 4.77 – 4.72 (m, 2H), 3.49 – 3.45 (m, 4H), 2.96 (d, J = 15.8 Hz, 6H), 2.67 (br d, J = 4.3 Hz, 4H), 1.47 (s, 9H).

Step 2

N,N-dimethyl-3-(piperazin-1-yl)oxacyclobutan-3-formamide **476b**

Compound **476a** (100 mg, 319.09 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (0.5 mL). The mixture was stirred at 25℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **476b** (70 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 214.2 [M+1]

Step 3

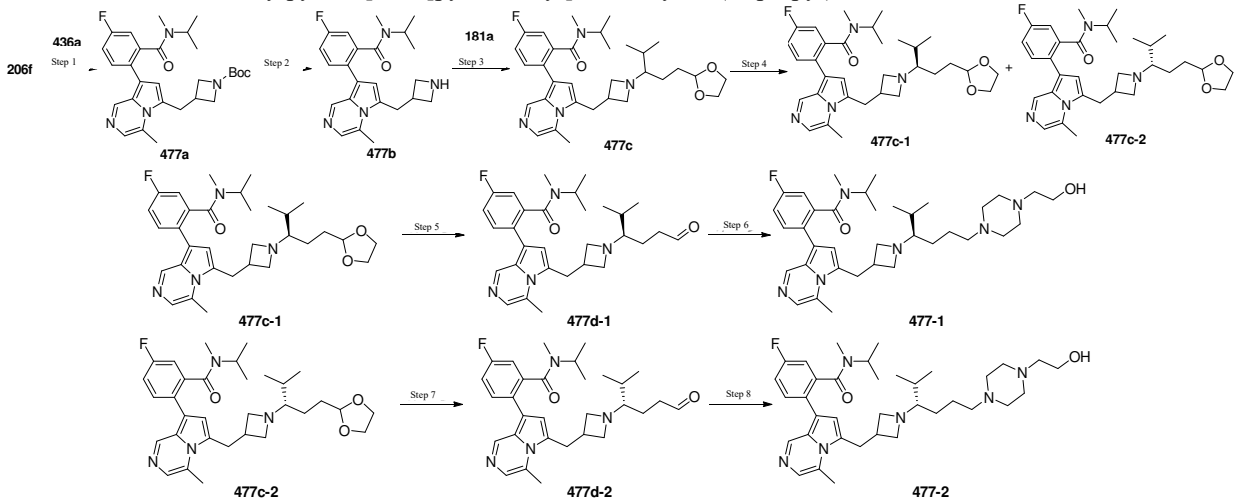
3-{4-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]piperazin-1-yl}-*N,N*-dimethyloxacyclobutan-3-formamide **476**

Compound **310b-2** (100 mg, 197.37 μmol) was dissolved in dichloromethane (5.0 mL), followed by the addition of triethylamine (39.94 mg, 394.75 μmol) and the crude product of Compound **476b** (70 mg). Under the protection of nitrogen, the mixture was stirred at 25℃ for 0.5 hours. Sodium cyanoborohydride (104.58 mg, 493.43 μmol) was added, allowing for reacting at 25℃ for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 36%-56%), to obtain the title Compound **476** (64.78 mg, 92.03 μmol, yield: 46.63%) as white solid.
MS m/z (ESI): 704.3 [M+1]
^{1}H NMR (400 MHz,DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.61 (m, 1H), 7.43 – 7.26 (m, 2H), 7.08 – 6.99 (m, 1H), 6.87 – 6.71 (m, 1H), 4.71 (s, 4H), 3.61 – 3.42 (m, 4H), 3.31 – 2.88 (m, 4H), 2.83 (s, 6H), 2.65 – 2.52 (m, 7H), 2.45 – 2.19 (m, 6H), 2.07 – 1.99 (m, 1H), 1.78 – 1.66 (m, 1H), 1.53 – 1.39 (m, 2H), 1.31 – 0.95 (m, 3H), 0.92 – 0.70 (m, 12H), 0.31 – 0.24 (m, 2H).

Examples 477-1 and 477-2

5-fluoro-2-[6-({1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-methyl-*N*-(isopropyl)benzamide **477-1**

5-fluoro-2-[6-({1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-methyl-*N*-(isopropyl)benzamide **477-2**



Step 1

3-[(8-{4-fluoro-2-[methyl(isopropyl)aminoformyl]phenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)methyl)azacyclobutan-1-tert-butyl carboxylate **477a**

Compound **206f** (1.2 g, 3.16 mmol), Compound **436a** (1.22 g, 3.79 mmol) and potassium phosphate (2.01 g, 9.47 mmol) were dissolved in dioxane (20 mL) and water (4.0 mL). Xphos Pd G4 (135.76 mg, 157.78 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 95°Cto allow for reacting for 2.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (30 mL) and extracting with ethyl acetate (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure.

The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **477a** (1.5 g, 3.03 mmol, yield: 96.11%) as yellow solid.
MS m/z (ESI): 495.5 [M+1]

Step 2

2-{6-[(azacyclobutan-3-yl)methyl]-4-methylpyrrolo[1,2-a]pyrazin-8-yl} -5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **477b**

Compound **477a** (1.5 g, 3.03 mmol) was dissolved in methane dioxide (15 mL), followed by the addition of trifluoroacetic acid (4.44 g, 38.94 mmol, 3 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (10.0 mL), regulated to PH = 10 by adding a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (30 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **477b** (1.2 g, 3.04 mmol, yield: 100.3%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 395.2 [M+1]

Step 3

2-[6-({1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl] -5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **477c**

Compound **477b** (1.2 g, 3.04 mmol) and Compound **181a** (628.66 mg, 3.65 mmol) were dissolved in methanol (20.0 mL). Acetic acid (182.68 mg, 3.04 mmol) was added, and the mixture was stirred at 40°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (573.49 mg, 9.13 mmol) and stirring at 40°C for 12.0 hour. A saturated aqueous sodium bicarbonate solution (25 mL) was added, and the mixture was then extracted with dichloromethane (25 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **477c** (800 mg, 1.45 mmol, yield: 47.75%) as yellow oil.
MS m/z (ESI): 551.5[M+1]

Step 4

2-[6-({1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **477c-1**

2-[6-({1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-5-fluoro-*N*-methyl-*N*-(isopropyl)benzamide **477c-2**

Compound **477c** (180 mg, 326.85 μmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: CO_2-MeOH (0.1% ammonia water); elution gradient: 25%), to obtain the title Compounds **477c-1** (70 mg, 127.11 μmol, yield: 38.89%) and **477c-2** (80 mg, 145.27 μmol, yield: 44.44%).

Single-configuration Compound 477c-1:
MS m/z (ESI):551.3 [M+1]
Chiral HPLC analysis: retention time: 1.166 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Single-configuration Compound 477c-2:
MS m/z (ESI):551.3[M+1]
Chiral HPLC analysis: retention time: 1.281 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: CO_2-MeOH (0.05% diethylamide): elution gradient: 5%-40%.

Step 5

5-fluoro-*N*-methyl-2-[4-methyl-6-({1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **477d-1**

Compound **477c-1** (70.00 mg, 127.11 μmol) was dissolved in acetonitrile (1.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 10 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **477d-1** (60 mg, 118.42 μmol, yield: 93.17%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 477d-1:
MS m/z (ESI): 507.3[M+1]

Step 6

5-fluoro-2-[6-({1-[(3*R*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-

methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-methyl-*N*-(isopropyl)benzamide **477-1**

The crude product of Compound **477d-1** (60.00 mg, 118.42 μmol) and 2-(piperazin-1-yl)ethanol (23.13 mg, 177.64 μmol) were dissolved in methanol (1 mL), followed by the addition of acetic acid (7.11 mg, 118.42 μmol), and the mixture was stirred at 40°C for 0.5 hours under the protection of nitrogen. Sodium cyanoborohydride (22.33 mg, 355.27 μmol) was added, allowing for reacting at 40°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title Compound **477-1** (25.31 mg, 40.77 μmol, yield: 34.42%).

Single-configuration Compound 477-1:

MS m/z (ESI):621.3 [M+1]

Chiral SFC: retention time: 1.156 min; chromatographic column: Chiralcel AD-3 50×4.6 mm I.D., 3 um; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 – 8.43 (m, 1H), 7.62 – 7.45 (m, 1H), 7.37 – 7.16 (m, 3H), 6.71 – 6.30 (m, 1H), 4.58 – 4.30 (m, 1H), 3.54 – 3.37 (m, 8H), 2.84 – 2.73 (m, 5H), 2.69 – 2.60 (m, 3H), 2.41 – 2.23 (m, 10H), 2.20 – 2.15 (m, 2H), 1.98 – 1.91 (m, 1H), 1.75 – 1.60 (m, 1H), 1.45 – 1.34 (m, 2H), 1.27 – 1.09 (m, 2H), 1.04 – 0.98 (m, 1H), 0.95 – 0.86 (m, 2H), 0.85 – 0.77 (m, 6H), 0.66 – 0.59 (m, 1H), 0.29 - -0.11 (m, 2H).

Step 7

5-fluoro-*N*-methyl-2-[4-methyl-6-({1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}methyl)pyrrolo[1,2-a]pyrazin-8yl]-*N*-(isopropyl)benzamide **477d-2**

Compound **477c-2** (80.00 mg, 145.27 μmol) was dissolved in acetonitrile (1.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 10 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **477d-2** (70 mg, 138.16 μmol, yield: 95.11%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 477d-2:

MS m/z (ESI): 507.3 [M+1]

Step 8

5-fluoro-2-[6-({1-[(3*S*)-6-[4-(2-hydroxylethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}methyl)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-methyl-*N*-(isopropyl)benzamide **477-2**

The crude product of Compound **477d-2** (70.00 mg, 138.16 μmol) and 2-(piperazin-1-yl)ethanol (26.98 mg, 207.24 μmol) were dissolved in methanol (2 mL), followed by the addition of acetic acid (8.30 mg, 138.16 μmol), and the mixture was stirred at 40°C for 0.5 hours under the protection of nitrogen.Sodium cyanoborohydride (26.05 mg, 414.48 μmol) was added, allowing for reacting at 40°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 26%-56%), to obtain the title Compound **477-2** (42.19 mg, 67.96 μmol, yield: 49.19%).

Single-configuration Compound 477-2:

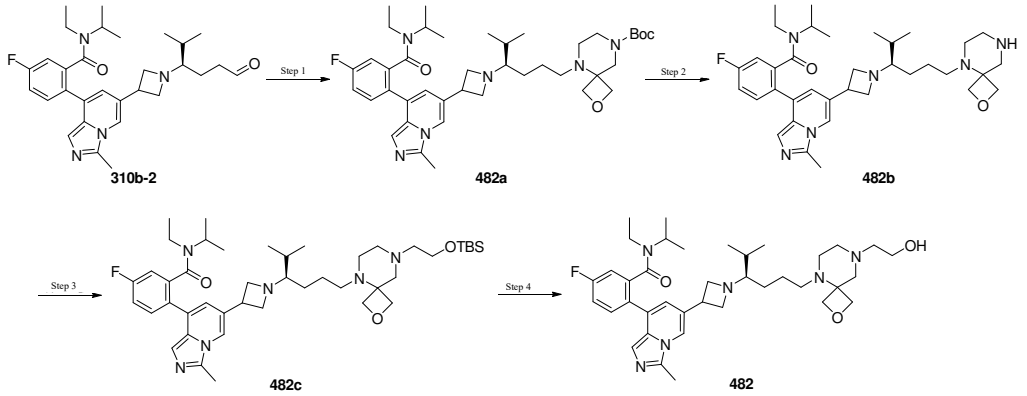
MS m/z (ESI):621.3 [M+1]

Chiral SFC: retention time: 1.391 min; chromatographic column: Chiralcel OD-3 50×4.6 mm I.D., 3um,; mobile phase: CO_2/MeOH (0.05% DEA): elution gradient: 5%-40%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 – 8.15 (m, 1H), 7.67 – 7.42 (m, 1H), 7.36 – 7.18 (m, 3H), 6.69 – 6.47 (m, 1H), 4.56 – 4.28 (m, 1H), 3.58 – 3.38 (m, 8H), 2.85 – 2.72 (m, 5H), 2.68 – 2.59 (m, 3H), 2.41 – 2.24 (m, 10H), 2.21 – 2.15 (m, 2H), 1.98 – 1.90 (m, 1H), 1.73 – 1.61 (m, 1H), 1.46 – 1.34 (m, 2H), 1.25 – 1.11 (m, 2H), 1.05 – 0.99 (m, 1H), 0.94 – 0.87 (m, 2H), 0.86 – 0.76 (m, 6H), 0.67 – 0.59 (m, 1H), 0.37 - -0.13 (m, 2H).

Example 482

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-[8-(2-hydroxyethyl)-2-oxa-5,8-diazaspiro[3.5]non-5-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **482**



Step 1

5-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-oxa-5,8-diazaspiro[3.5]nonan-8-tert-butyl carboxylate **482a**

Compound **310b-2** (200 mg, 394.75 μmol) and 2-oxa-5,8-diazaspiro[3.5]nonan-8-tert-butyl carboxylate (108.14 mg, 473.70 μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (23.70 mg, 394.75 μmol), and the mixture was stirred at 35°C for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (74.42 mg, 1.18 mmol) was added, and the mixture was stirred at 35℃ to allow for reacting for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (65 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **482a** (120 mg, 166.91 μmol, yield: 42.28%) as yellow oil.

MS m/z (ESI):719.3 [M+1]

Step 2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-{2-oxa-5,8-diazaspiro[3.5]non-5-yl}hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **482b**

Compound **482a** (100 mg, 139.09 μmol) was dissolved in dichloromethane (1.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 25℃. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, regulated to PH = 14 by adding a 10%aqueous sodium hydroxide solution in an ice bath, and extracted with dichloromethane (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **482b** (100 mg, 161.60 μmol, yield: 116.18%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI):619.4 [M+1]

Step 3

2-(6-{1-[(3*R*)-6-(9-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-2-oxa-5,8-diazaspiro[3.5]non-5-yl)-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **482c**

Compound **482b** (100 mg, 161.60 μmol)) and 2-[tert-butyl(dimethyl)silicyl]oxyacetaldehyde (33.80 mg, 193.92 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (9.70 mg, 161.60 μmol), and the mixture was stirred at 35°C for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (30.47 mg, 484.79 μmol) was added, and the mixture was stirred at 35℃ to allow for reacting for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (65 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **482c** (100 mg, 128.68 μmol, yield: 79.63%) as yellow solid. The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI):777.4 [M+1]

Step 4

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-[8-(2-hydroxyethyl)-2-oxa-5,8-diazaspiro[3.5]non-5-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **482**

482c (100 mg, 128.68 μmol) was dissolved in trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL), and the mixture was stirred at 25°C for 0.5 hours.The reaction mixture was diluted with ethyl acetate (20 mL), and washed with a saturated aqueous sodium carbonate solution (20 mL x 3), and the organic phase was concentrated under a reduced pressure. The obtained crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water),

elution gradient:28%-58%). The title Compound **482** (12.24 mg, 18.46 μmol, yield: 14.35%) was obtained as yellow solid.

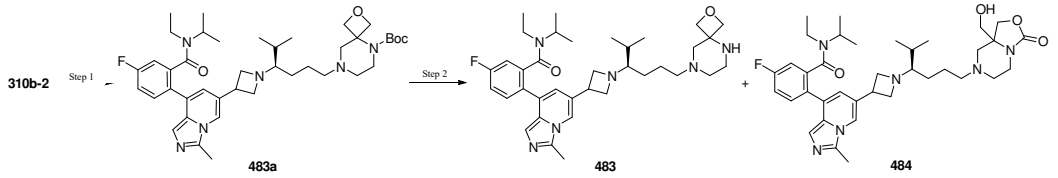
MS m/z (ESI): 663.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.70 – 7.64 (m, 1H), 7.42 – 7.33 (m, 1H), 7.33 – 7.28 (m, 1H), 7.06 – 7.01 (m, 1H), 6.75 (d, J = 15.6 Hz, 1H), 4.53 (d, J = 6.4 Hz, 2H), 4.38 (t, J = 5.2 Hz, 1H), 4.15 (d, J = 6.4 Hz, 2H), 3.61 – 3.41 (m, 6H), 3.30 – 3.27 (m, 1H), 3.19 – 3.03 (m, 2H), 2.97 – 2.89 (m, 1H), 2.64 – 2.53 (m, 7H), 2.45 – 2.39 (m, 2H), 2.38 – 2.30 (m, 4H), 2.08 – 2.00 (m, 1H), 1.77 – 1.66 (m, 1H), 1.52 – 1.39 (m, 2H), 1.34 – 1.21 (m, 2H), 0.94 – 0.70 (m, 13H), 0.30 – 0.24 (m, 2H).

Examples 483 and 484

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-{2-oxa-5,8-diazaspiro[3.5]non-8-yl}hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **483**

2-(6-{1-[(3*R*)-6-[8^a-(hydroxymethyl)-3-oxo-hexahydro-1*H*-[1,3]oxazolo[3,4-a]pyrazin-7-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **484**



Step 1

8-[(4*R*)-4-[3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-oxa-5,8-diazaspiro[3.5]nonan-5-tert-butyl carboxylate **483a**

Compound **310b-2** (200 mg, 394.75 μmol) and 2-oxa-5,8-diazaspiro[3.5]nonan-5-tert-butyl carboxylate (90.12 mg, 394.75 μmol) were dissolved in methanol (5.0 mL), followed by the addition of sodium cyanoborohydride (74.42 mg, 1.18 mmol), and the mixture was stirred at 50°C for 1.0 hour under the protection of nitrogen. Sodium cyanoborohydride (74.42 mg, 1.18 mmol) was further added, and the mixture was stirred at 50°C to allow for reacting for 2 hours under the protection of nitrogen. The reaction mixture was concentrated under a reduced pressure to remove the organic solvent, followed by adding a saturated aqueous potassium carbonate solution (10 mL) and extracting with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title product **483a** (127 mg, 176.65 μmol, yield: 44.75%) as yellow solid.

MS m/z (ESI):719.6 [M+1]

Step 2

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-{2-oxa-5,8-diazaspiro[3.5]non-8-yl}hexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **483**

2-(6-{1-[(3*R*)-6-[8^a-(hydroxymethyl)-3-oxo-hexahydro-1*H*-[1,3]oxazolo[3,4-a]pyrazin-7-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **484**

Compound **483a** (97 mg, 134.92 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 25°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding DCM (5 mL), regulated to PH > 7 by adding triethylamine, and concentrated under a reduced pressure. The crude product was purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient:28%-58%), to obtain the title Compounds **483** (14.27 mg, 23.06 μmol, yield: 17.09%) and **484** (18.72 mg, 28.24 μmol, yield: 20.93%).

Compound **483:**

MS m/z (ESI):619.4 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1 H), 7.61 – 7.74 (m, 1 H), 7.38 (td, J=8.40, 2.80 Hz, 1 H), 7.27 – 7.34 (m, 1 H), 6.99 – 7.07 (m, 1 H), 6.75 (d, J=15.60 Hz, 1 H), 4.35 – 4.51 (m, 2 H), 4.22 – 4.29 (m, 4 H), 3.45 – 3.53 (m, 2 H), 3.29 (br s, 1 H), 3.14 (br dd, J=14.01, 6.40 Hz, 1 H), 3.07 (br d, J=7.60 Hz, 1 H), 2.92 (dq, J=13.60, 6.80 Hz, 1 H), 2.58 (s, 5 H) ,2.45 (br s, 1 H), 2.17 – 2.29 (m, 4 H), 2.07 (s, 2 H), 2.02 – 2.06 (m, 1 H), 1.71 (br d, J=6.80 Hz, 1 H), 1.46 (br d, J=6.40 Hz, 2 H), 1.19 – 1.26 (m, 2 H), 0.71 – 0.91 (m, 13 H), 0.28 (br d, J=6.40 Hz, 2 H).

Compound **484:**

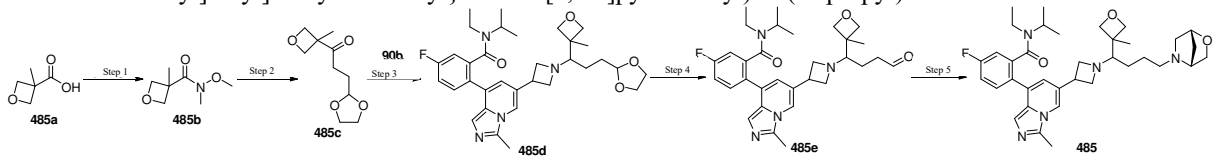
MS m/z (ESI):663.2 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1 H), 7.62 – 7.73 (m, 1 H), 7.27 – 7.44 (m, 2 H), 6.98 – 7.08 (m, 1 H), 6.76 (d, J=12.40 Hz, 1 H), 5.00 (t, J=5.60 Hz, 1 H), 4.14 – 4.24 (m, 1 H), 3.84 (br d, J=8.40 Hz, 1 H), 3.71 – 3.79 (m, 1 H), 3.40 – 3.61 (m, 6 H), 3.26 – 3.31 (m, 1 H), 3.10 – 3.18 (m, 1 H), 2.88 – 3.09 (m, 3 H), 2.85 (br d, J=11.20 Hz,

1 H), 2.70 – 2.77 (m, 1 H), 2.59 (s, 3 H), 2.19 – 2.33 (m, 2 H), 2.02 (br s, 1 H), 1.77 – 1.89 (m, 2 H), 1.65 – 1.76 (m, 1 H), 1.37 – 1.50 (m, 2 H), 1.14 – 1.31 (m, 2 H), 0.66 – 1.01 (m, 13 H), 0.27 (br d, J=5.20 Hz, 2 H).

Example 485

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[1-(3-methyloxacyclobutan-3-yl)-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]butyl]azacyclobut-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **485**



Step 1

N-methoxy-*N*,3-dimethyloxacyclobutan-3-formamide **485b**

3-Methyloxacyclobutan-3-carboxylic acid **485a**(1 g, 8.61 mmol), *N*-methoxymethylamine (1.68 g, 17.22 mmol, hydrochloride), HATU (3.60 g, 9.47 mmol) and triethylamine (2.61 g, 25.84 mmol) were dissolved in DMF (10 mL). The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the title Compound **485b** (790 mg, 4.96 mmol, yield: 57.63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (d, J = 6.4 Hz, 2H), 4.28 (d, J = 6.4 Hz, 2H), 3.66 (s, 3H), 3.18 (s, 3H),1.66(s,3H).

Step 2

3-(1,3-dioxolan-2-yl)-1-(3-methyloxacyclobutan-3-yl)propan-1-one **485c**

Under the protection of nitrogen, Compound **485b** (790 mg, 4.96 mmol) was dissolved in tetrahydrofuran (10.0 mL), and cooled to -0°C under the protection of nitrogen, followed by the slow dropwise addition of magnesium 2-(1,3-dioxolan-2-yl)ethyl bromide solution (0.5 M, 17.41 mL). After the dropwise addition, the mixture was further stirred 0°C for 1.0 hour, then warmed to 25°C and further stirred for 12 hours. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (30 mL), and extracted with methyltert-butyl ether (20 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **485c** (410 mg, 2.05 mol, yield: 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 – 4.91 (m, 1H), 4.89 (d, J = 6.0 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H), 3.98 – 3.93 (m, 2H), 3.88 – 3.83 (m, 2H), 2.66 – 2.58 (m, 2H), 2.03 (td, J = 3.6, 7.2 Hz, 2H), 1.56 (s, 3H).

Step 3

2-(6-{1-[3-(1,3-dioxolan-2-yl)-1-(3-methyloxacyclobutan-3-yl)propyl]azacyclobut-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **485d**

Compound **90b** (290 mg, 735.14 μmol) and Compound **485c** (273.37 mg, 955.68 μmol) were dissolved in methanol (2.0 mL), followed by the addition of $ZnCl_2$ (200.39 mg, 1.47 mmol), and the mixture was stirred at 50°C for 1.0 hour. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (138.59 mg, 2.21 mmol) and stirring at 50°C for 12 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **485d** (165 mg, 285.11 μmol, yield: 38.78%) as yellow solid.

MS m/z (ESI): 579.4 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.58 – 7.50 (m, 1H), 7.23 – 7.10 (m, 3H), 6.88 – 6.76 (m, 1H), 4.89 – 4.72 (m, 2H), 4.68 – 4.59 (m, 1H), 4.16 (d, J = 5.2 Hz, 2H), 4.01 – 3.92 (m, 2H), 3.89 – 3.81 (m, 2H), 3.77 – 3.66 (m, 1H), 3.60 – 3.42 (m, 4H), 3.30 – 3.10 (m, 2H), 3.01 – 2.87 (m, 1H), 2.75 (d, J = 2.4 Hz, 1H), 2.68 (s, 3H), 1.67 (br dd, J = 4.4, 7.6 Hz, 1H), 1.56 – 1.42 (m, 5H), 1.29 – 1.10 (m, 2H), 1.00 – 0.89 (m, 5H), 0.78 (br t, J = 7.2 Hz, 1H), 0.26 (dd, J = 2.8, 6.4 Hz, 2H).

Step 4

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[1-(3-methyloxacyclobutan-3-yl)-4-oxobutyl]azacyclobutan-3-alkyl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **485e**

Compound **485d** (50 mg, 86.40 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (0.5 mL). The mixture was stirred at 25°C to allow for reacting for 1.0 hours. The reaction mixture was regulated to pH = 8-9 with a saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (8 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **485e** (40 mg, 74.81 μmol, yield: 86.59%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 535.4 [M+1]

Step 5

N-ethyl-5-fluoro-2-(3-methyl-6-{1-[1-(3-methyloxacyclobutan-3-yl)-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]butyl]azacyclobut-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **485**

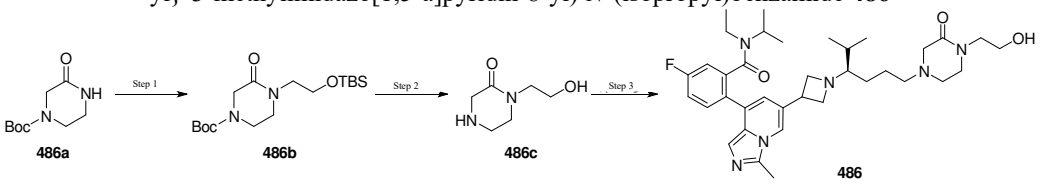
Compound **485e** (40 mg, 74.81 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of triethylamine (15.14 mg, 149.63 μmol) and (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (12.17 mg, 89.78 μmol, hydrochloride). Under the protection of nitrogen, the mixture was stirred at 50℃ for 1.0 hours. Sodium cyanoborohydride (47.57 mg, 224.44 μmol) was added, allowing for reacting at 50℃ for 16 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 21%-41%), to obtain the title Compound **485** (11.14 mg, 18.03 μmol, yield: 24.10%) as yellow solid.

MS m/z (ESI): 618.3 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.55 – 7.50 (m, 1H), 7.22 – 7.12 (m, 3H), 6.93 – 6.80 (m, 1H), 4.88 – 4.71 (m, 1H), 4.60 (d, J = 5.2 Hz, 1H), 4.39 (s, 1H), 4.16 (d, J = 4.8 Hz, 2H), 4.08 – 3.99 (m, 1H), 3.74 – 3.61 (m, 2H), 3.60 – 3.39 (m, 5H), 3.27 – 3.11 (m, 2H), 2.99 – 2.86 (m, 2H), 2.75 – 2.70 (m, 1H), 2.68 (s, 3H), 2.61 – 2.41 (m, 3H), 1.87 – 1.73 (m, 2H), 1.45 (s, 3H), 1.39 – 1.28 (m, 3H), 1.20 – 1.09 (m, 2H), 1.00 – 0.84 (m, 6H), 0.27 – 0.24 (m, 2H).

Example 486

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **486**



Step 1

4-{2-[(tert-butyldimethylsilicyl)oxy]ethyl}-3-oxopiperazin-1-tert-butyl carboxylate **486b**

3-Oxopiperazin-1-tert-butyl carboxylate **486a** (1 g, 4.99 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (1.19 g, 4.99 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of potassium hydroxide (336.24 mg, 5.99 mmol) and tetrabutylammonium iodide (368.93 mg, 998.83 μmol). The reaction mixture was stirred at 25°C for 12 hours, the reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **486b** (500 mg, 1.39 mmol, yield: 27.92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 2H), 3.71 – 3.66 (m, 2H), 3.55 – 3.49 (m, 2H), 3.43 – 3.37 (m, 4H), 1.42 – 1.38 (m, 9H), 0.87 – 0.83 (m, 9H), 0.05-0.02 (m, 6H).

Step 2

1-(2-hydroxyethyl)piperazin-2-one **486c**

Compound **486b** (150 mg, 418.36 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25°C for 4.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **486c** (60 mg). The crude product was directly used in the next step of reaction without purification.

^{1}H NMR (400 MHz, CD_3OD) δ 4.26 – 4.21 (m, 1H), 3.53 – 3.47 (m, 2H), 3.44 – 3.31 (m, 4H), 3.27 – 3.13 (m, 2H), 3.01 – 2.90 (m, 2H).

Step 3

N-ethyl-5-fluoro-2-(6-{1-[(3*R*)-6-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-(isopropyl)benzamide **486**

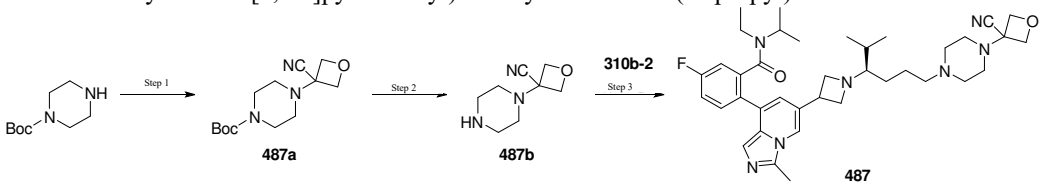
Compound **310b-2**(135 mg, 266.45 μmol) was dissolved in methanol (5.0 mL), followed by the addition of triethylamine (53.92 mg, 532.91 μmol) and the crude product of Compound **486c** (60 mg). Under the protection of nitrogen, the mixture was stirred at 40℃ for 0.5 hours. Sodium cyanoborohydride (50.23 mg, 799.36 μmol) was added, allowing for reacting at 40℃ for 12 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (15 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 25%-55%), to obtain the title Compound **486** (23.17 mg, 36.50 μmol, yield: 13.70%) as yellow solid.

MS m/z (ESI): 635.2 [M+1]

^{1}H NMR (400 MHz,DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.63 (m, 1H), 7.45 – 7.23 (m, 2H), 7.10 – 6.96 (m, 1H), 6.89 – 6.71 (m, 1H), 4.76 – 4.61 (m, 1H), 3.63 – 3.38 (m, 7H), 3.31 – 3.03 (m, 6H), 2.98 – 2.84 (m, 3H), 2.63 – 2.54 (m, 5H), 2.34 – 2.24 (m, 2H), 2.12 – 1.96 (m, 1H), 1.79 – 1.65 (m, 1H), 1.55 – 1.39 (m, 2H), 1.32 – 1.02 (m, 3H), 0.93 – 0.70 (m, 12H), 0.30 – 0.26 (m, 2H).

Example 487

2-(6-{1-[(3*R*)-6-[4-(3-cyanooxacyclobutan-3-yl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **487**



Step 1

4-(3-cyanooxacyclobutan-3-yl)piperazin-1-tert-butyl carboxylate **487a**

Piperazin-1-tert-butyl carboxylate (3 g, 16.11 mmol) and oxacyclobutan-3-one (1.74 g, 24.16 mmol) were dissolved in 1,2-dichloroethane (40 mL), followed by the addition of acetic acid (1.16 g, 19.33 mmol), and the reaction mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by the dropwise addition of TMSCN(3.49 g, 35.18 mmol), and the reaction mixture was stirred at 25°C for 16 hours. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **487a** (3.14 g, 11.75 mmol, yield: 72.92%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, J=6.40 Hz, 2 H), 4.65 (d, J=6.40 Hz, 2 H), 3.43 – 3.57 (m, 4 H), 2.36 (br s, 4 H), 1.45 (s, 9 H).

Step 2

3-(piperazin-1-yl)oxacyclobutan-3-nitrile **487b**

Compound **487a** (200 mg, 748.16 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL). The mixture was stirred at 25°C for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, and the residues were dissolved with dichloromethane (10 mL) and regulated to PH = 8 with triethylamine. The mixture was concentrated under a reduced pressure to remove the solvent, to obtain the crude product of title Compound **487b** (130 mg). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 168.3 [M+1]

Step 3

2-(6-{1-[(3*R*)-6-[4-(3-cyanooxacyclobutan-3-yl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **487**

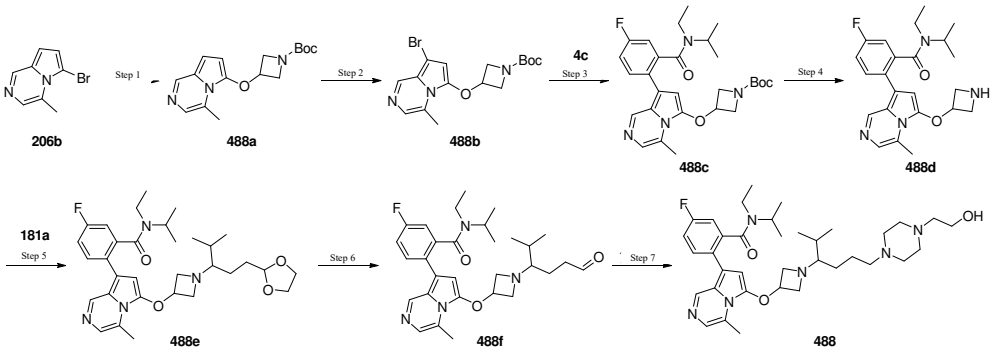
Compound **310b-2** (130 mg, 256.59 μmol) was dissolved in methanol (3.0 mL), followed by the addition of the crude product of Compound **487b** (130 mg). Under the protection of nitrogen, the mixture was stirred at 50℃ for 1.0 hours. Sodium cyanoborohydride (80.62 mg, 1.28 mmol) was added, allowing for reacting 50℃ for 16 hours under the protection of nitrogen. A saturated aqueous potassium carbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 0%-26%), to obtain the title Compound **487** (8.92 mg, 13.56 μmol, yield: 5.28%) as yellow solid.

MS m/z (ESI): 658.5 [M+1]

^{1}H NMR (400 MHz,DMSO-d_6) δ 8.20 (br s, 2 H), 7.96 (br s, 1 H), 7.61 – 7.74 (m, 1 H), 7.28 – 7.43 (m, 2 H), 6.99 – 7.08 (m, 1 H), 6.71 – 6.89 (m, 1 H), 4.71 (br d, J=6.80 Hz, 2 H), 4.55 (br d, J=6.40 Hz, 2 H), 3.58 (br d, J=6.80 Hz, 3 H), 3.41 – 3.47 (m, 1 H), 3.23 – 3.34 (m, 3 H), 2.85 – 2.95 (m, 1 H), 2.59 (s, 3 H), 2.44 (br s, 3 H), 2.21 – 2.37 (m, 7 H), 1.77 (br s, 1 H), 1.47 (br s, 2 H), 1.18 – 1.32 (m, 2 H), 1.06 (br s, 1 H), 0.68 – 0.91 (m, 13 H), 0.27 (br d, J=6.40 Hz, 2 H).

Example 488

N-ethyl-5-fluoro-2-{6-[(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)oxy]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-*N*-(isopropyl)benzamide **488**



Step 1

3-({4-methylpyrrolo[1,2-a]pyrazin-6-yl}oxy)azacyclobutan-1-tert-butyl carboxylate **488a**

Compound 3-hydroxylazacyclobutan-1-tert-butyl formate (3.04 g, 17.53 mmol) was dissolved in DMSO(50 mL), and cooled to 0°C, followed by the slow addition of NaH (1.05 g, 26.30 mmol, 60%purity), and the mixture was stirred at 25°C to allow for reacting for 0.5 hours. Compound **206b** (3.7 g, 17.53 mmol) was added, and the mixture was stirred at 80°C under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was cooled to room temperature, followed by the addition of a saturated aqueous ammonium chloride solution (50 mL), and the reaction mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **488a** (160 mg, 527.43 μmol, yield: 3.01%) as yellow solid.

MS m/z (ESI): 304.2 [M+1]

Step 2

3-({8-bromo-4-methylpyrrolo[1,2-a]pyrazin-6-yl}oxy)azacyclobutan-1-tert-butyl carboxylate **488b**

Compound **488a** (200 mg, 659.29 μmol) was dissolved in dichloromethane (3.0 mL), and cooled to -10°C, followed by the addition of NBS(117.34 mg, 659.29 μmol), and the mixture was stirred at room temperature for 1.0 hour. A saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction mixture, which was then extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **488b** (160 mg, 418.57 μmol, yield: 63.49%) as yellow solid.

MS m/z (ESI): 384.0 [M+1]

Step 3

3-[(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-4-methylpyrrolo[1,2-a]pyrazin-6-yl)oxy]azacyclobutan-1-tert-butyl carboxylate **488c**

Compound **488b** (160 mg, 418.57 μmol), Compound **4c**(210.47 mg, 627.86 μmol) and potassium phosphate (266.55 mg, 1.26 mmol) were dissolved in dioxane (0.5 mL) and water (0.1 mL). $Pd(dtbpf)Cl_2$ (27.28 mg, 41.86 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 3.0 hours. The reaction mixture was cooled to room temperature, diluted by adding ethyl acetate (20 mL), and washed with water (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **488c** (170 mg, 332.94 μmol, yield: 79.54%) as yellow solid.

MS m/z (ESI): 511.2 [M+1]

Step 4

2-[6-(azacyclobutan-3-yloxy)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **488d**

Compound **488c** (170 mg, 332.94 μmol) was dissolved in methane dioxide (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a 10% aqueous sodium hydroxide solution (10.0 mL) and extracting with dichloromethane (10 mL x 2). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **488d** (140 mg, 341.06 μmol, yield: 102.44%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 411.2 [M+1]

Step 5

2-[6-({1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}oxy)-4-methylpyrrolo[1,2-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **488e**

Compound **488d** (120 mg, 292.34 μmol) and Compound **181a** (60.42 mg, 350.81 μmol) were dissolved in methanol (3.0 mL). Acetic acid (17.55 mg, 292.34 μmol) was added, and the mixture was stirred at 50℃ for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (55.11 mg, 877.01 μmol) and stirring at 50℃ for 11.0 hours. The mixture was diluted with ethyl acetate (20 mL), and washed with water (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **488e** (30 mg, 52.94 μmol, yield: 18.11%) as yellow oil.
MS m/z (ESI): 567.2[M+1]

Step 6

N-ethyl-5-fluoro-2-(4-methyl-6-{[1-(2-methyl-6-oxohexan-3-yl)azacyclobutan-3-yl]oxy}pyrrolo[1,2-a]pyrazin-8-yl)-*N*-(isopropyl)benzamide **488f**

Compound **488e** (20 mg, 35.29 μmol) was dissolved in acetonitrile (0.5 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 0.5 mL). The mixture was stirred at 50℃ to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding an aqueous saturated potassium carbonate solution (10 mL) and extracting with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **488f** (18 mg, 34.44 μmol, yield: 97.59%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 523.4[M+1]

Step 7

N-ethyl-5-fluoro-2-{6-[(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)oxy]-4-methylpyrrolo[1,2-a]pyrazin-8-yl}-*N*-(isopropyl)benzamide **488**

The crude product of Compound **488f** (18 mg, 34.44 μmol) and 2-(piperazin-1-yl)ethanol (5.38 mg, 41.33 μmol) were dissolved in methanol (2.0 mL), followed by the addition of acetic acid (2.07 mg, 34.44 μmol), under the protection of nitrogen, and the mixture was stirred at 50℃ for 1.0 hour. Sodium cyanoborohydride (6.49 mg, 103.32 μmol) was added, allowing for reacting at 50℃ for 11.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 38%-68%), to obtain the title Compound **488** (15.23 mg, 23.91 μmol, yield: 69.44%).
MS m/z (ESI):637.5 [M+1]
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.56 – 7.50 (m, 1H), 7.35 – 7.28 (m, 1H), 7.27 – 7.20 (m, 1H), 7.07 (s, 1H), 6.27 – 6.20 (m, 1H), 4.82 – 4.73 (m, 1H), 4.41 – 4.23 (m, 1H), 3.73 – 3.60 (m, 2H), 3.49 – 3.43 (m, 2H), 3.42 – 3.37 (m, 1H), 3.30 – 3.22 (m, 1H), 3.12 – 2.93 (m, 3H), 2.66 (s, 3H), 2.42 – 2.25 (m, 9H), 2.22 – 2.17 (m, 2H), 2.07 – 2.00 (m, 1H), 1.75 – 1.64 (m, 1H), 1.47 – 1.34 (m, 2H), 1.28 – 1.07 (m, 3H), 0.93 – 0.76 (m, 12H), 0.74 – 0.68 (m, 1H), 0.35 – 0.30 (m, 2H).

Example 490

2-(6-{1-[(3R)-6-{4-[3-(cyanomethyl)oxacyclobutan-3-yl]piperazin-1-yl}-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **490**

Step 1

4-[3-(cyanomethyl)oxacyclobutan-3-yl]piperazin-1-tert-butyl carboxylate **490a**

Piperazin-1-tert-butyl carboxylate (220.00 mg, 1.18 mmol) and 2-(oxacyclobutan-3-methylene)acetonitrile (123.56 mg, 1.30 mmol) were dissolved in acetonitrile (2.0 mL), followed by the addition of DBU(215.79 mg, 1.42 mmol), and the reaction mixture was stirred at 25°C for 12 hours. The reaction mixture was cooled to room temperature, followed by the dropwise addition of TMSCN(3.49 g, 35.18 mmol), and the reaction mixture was stirred at 25°C for 16 hours. Water (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **490a** (100 mg, 355.43 μmol, yield: 30.09%) as white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 4.46 (d, J = 6.4 Hz, 2H), 4.36 (d, J = 6.4 Hz, 2H), 3.34 – 3.32 (m, 2H), 3.32 – 3.29

(m, 2H), 2.96 (s, 2H), 2.36 – 2.29 (m, 4H), 1.39 (s, 9H).

Step 2

2-[3-(piperazin-1-yl)oxacyclobutan-3-yl]acetonitrile **490b**

Compound **490a** (45 mg, 159.94 μmol) was dissolved in dichloromethane (1.5 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL). The mixture was stirred at 25°C for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, to obtain the crude product of title Compound **490b** (28 mg). The crude product was directly used in the next step of reaction without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J = 6.8 Hz, 2H), 4.50 (d, J = 6.8 Hz, 2H), 3.40 (t, J = 4.8 Hz, 4H), 2.92 (s, 2H), 2.89 (t, J = 4.8 Hz, 4H).

Step 3

2-(6-{1-[(3R)-6-{4-[3-(cyanomethyl)oxacyclobutan-3-yl]piperazin-1-yl}-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **490**

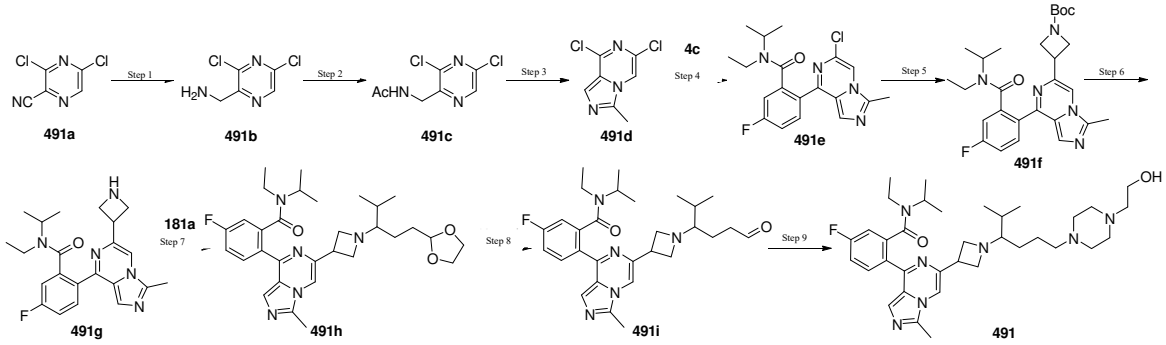
Compound **310b-2** (70 mg, 138.16 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of the crude product of Compound **490b** (28 mg) and triethylamine (41.94 mg, 414.48 μmol). Under the protection of nitrogen, the mixture was stirred at 25°C for 1.0 hours. Sodium cyanoborohydride (87.85 mg, 414.48 μmol) was added, allowing for reacting at 25°C for 11 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (10 mM ammonium acetate), elution gradient: 29%-59%), to obtain the title Compound **490** (29.49 mg, 43.89 μmol, yield: 31.77%) as yellow solid.

MS m/z (ESI): 672.5 [M+1]

^{1}H NMR (400 MHz,CD_3OD) δ 7.94 – 7.90 (m, 1H), 7.77 – 7.69 (m, 1H), 7.34 (dt, J = 2.8, 8.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.17 – 7.12 (m, 1H), 6.95 – 6.87 (m, 1H), 4.61 (dd, J = 3.2, 6.4 Hz, 2H), 4.50 – 4.45 (m, 2H), 3.84 – 3.32 (m, 6H), 3.30 – 3.24 (m, 1H), 3.10 – 2.99 (m, 1H), 2.96 (d, J = 4.4 Hz, 2H), 2.66 (s, 3H), 2.62 – 2.32 (m, 10H), 2.31 – 2.24 (m, 1H), 1.92 – 1.82 (m, 1H), 1.68 – 1.53 (m, 2H), 1.47 – 1.09 (m, 3H), 0.98 – 0.77 (m, 12H), 0.30 (d, J = 6.4 Hz, 2H).

Example 491

N-ethyl-5-fluoro-2-[6-(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **491**



Step 1

1-(3,5-dichloropyrazin-2-yl)methylamine **491b**

Under an argon atmosphere, Raney Ni (0.5 g, 5.75 mmol) and 3,5-dichloropyrazin-2-nitrile **491a** (1 g, 5.75 mmol) were dissolved in acetic acid (20 mL), and the reaction mixture was added to a stainless steel hydrogenation flask. Hydrogen substitution was carried out three times, and under a hydrogen atmosphere (50 PSI), the reaction mixture was stirred at 50°C to allow for reacting for 12 hours. The reaction mixture was filtered through diatomite, and the filter cake was washed with methanol. The filtrate was concentrated under a reduced pressure, to obtain the crude product of title Compound **491b** (1.02 g, 5.73 mmol, yield: 99.7%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 179.1 [M+1]

Step 2

N-[(3,5-dichloropyrazin-2-yl)methyl]acetamide **491c**

Compound **491b** (1.95 g, 10.95 mmol) was dissolved in dichloromethane (60 mL), followed by the addition of triethylamine (4.43 g, 43.82 mmol). The reaction mixture was cooled to 0°C, followed by the slow dropwise addition of acetic anhydride (1.68 g, 16.43 mmol), and the reaction mixture was stirred at room temperature to allow for reacting for 12 hours. The reaction mixture was diluted by adding water (50 mL), the organic phase and the aqueous

phase were separated, and the aqueous phase was extracted with ethyl acetate (40 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **491c** (1.04 g, 4.73 mmol, yield: 43.15%) as yellow oil.
MS m/z (ESI): 220.1 [M+1]

Step 3

6,8-dichloro-3-methylimidazol[1,5-a]pyrazine **491d**

Compound **491c** (990 mg, 4.50 mmol) was dissolved in dichloromethane (10.0 mL), followed by the addition of a Burgess reagent (1.61 g, 6.75 mmol). The mixture was stirred at 40℃ to allow for reacting for 4.0 hours. The reaction mixture was cooled to room temperature, followed by adding water (50 mL) and extracting with ethyl acetate (50 mL x 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **491d** (680 mg, 3.37 mmol, yield: 74.81%) as yellow solid.
MS m/z (ESI): 204.1[M+1]

Step 4

2-{6-chloro-3-methylimidazo[1,5-a]pyrazin-8-yl}-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **491e**

Compound **491d** (250 mg, 1.24 mmol), Compound **4c**(373.31 mg, 1.11 mmol) and potassium phosphate (525.31 mg, 2.47 mmol) were dissolved in dioxane (10 mL) and water (2.0 mL). Pd (dppf)Cl_2 (90.54 mg, 123.74 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 25°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using petroleum ether/ethyl acetate as an elution system, to obtain the title Compound **491e** (350 mg, 933.73 μmol, yield: 75.46%) as yellow solid.
MS m/z (ESI): 375.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.26 – 7.08 (m, 2H), 4.45 – 3.94 (m, 1H), 3.48 – 3.20 (m, 2H), 2.69 (s, 3H), 1.34 – 1.14 (m, 9H).

Step 5

3-(8-{2-[ethyl(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyrazin-6-yl)azacyclobutan-1-tert-butyl carboxylate **491f**

Compound **491e** (347 mg, 925.73 μmol), nickel(II) chloride ethylene glycol dimethyl ether complex (30.51 mg, 138.86 μmol), pyridin-2,6-bis(carboximidamide) dihydrochloride (32.78 mg, 138.86 μmol) and sodium iodide (34.69 mg, 231.43 μmol) were dissolved in DMF(5.0 mL). Under a nitrogen atmosphere, 3-bromoazacyclobutan-1-tert-butyl formate (382.50 mg, 1.62 mmol), Mn(152.57 mg, 2.78 mmol) and trifluoroacetic acid (10.56 mg, 92.57 μmol) were added. The reaction mixture was heated to 60°C, and stirred under a nitrogen atmosphere to allow for reacting for 12.0 hours. The reaction mixture was quenched by adding ammonia water (10 mL), diluted with ethyl acetate (20 mL x) and then filtered, and the filter cake was washed with ethyl acetate. The organic phase of the filtrate was washed with water, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the HPLC (mobile phase: acetonitrile, water (0.1% ammonia water), elution gradient: 31%-61%), to obtain the title Compound **491f** (60 mg, 121.07 μmol, yield: 13.08%). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 496.2 [M+1]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 5.3, 8.6 Hz, 1H), 7.61 (s, 1H), 7.45 – 7.40 (m, 1H), 7.26 – 7.11 (m, 2H), 4.29 – 4.21 (m, 2H), 4.19 – 4.09 (m, 2H), 4.08 – 3.98 (m, 1H), 3.86 – 3.75 (m, 1H), 3.43 – 3.15 (m, 2H), 2.67 (s, 3H), 1.46 (s, 9H), 1.26 – 1.02 (m, 9H).

Step 6

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyrazin-8-yl]-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **491g**

Compound **491f** (80 mg, 161.42 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0℃. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding dichloromethane (10 mL), regulated to PH = 10 with 10% aqueous sodium hydroxide solution, and extracted with dichloromethane/isopropanol (10/1, 10 mL x 5), and the organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **491g** (51 mg). The crude product was directly used in the next step of reaction without purification.
MS m/z (ESI): 396.6 [M+1]

Step 7

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyrazin-8-yl)-*N*-ethyl-5-fluoro-*N*-(isopropyl)benzamide **491h**

The crude product of Compound **491g** (51 mg) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (28.74 mg, 141.86 μmol) were dissolved in methanol (5 mL), followed by the addition of $ZnCl_2$ (35.15 mg, 257.92 μmol), and the mixture was stirred at 50°C for 1.0 hour. The reaction mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (24.31 mg, 386.88 μmol) and stirring at 50°C for 11 hours. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **4191h** (44 mg, 79.75 μmol, yield: 61.84%).

MS m/z (ESI): 552.4 [M+1]

Step 8

N-ethyl-5-fluoro-2-{3-methyl-6-[1-(2-methyl-6-oxohexan-3-yl)azacyclobutan-3-yl]imidazo[1,5-a]pyrazin-8-yl}-*N*-(isopropyl)benzamide **491i**

Compound **491h** (44 mg, 79.75 μmol) was dissolved in acetonitrile (3.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 1.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding dichloromethane (5 mL) and water (5 mL), regulating to pH = 10 with a 10 % aqueous NaOH solution and extracting with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **491i** (40 mg, 78.80 μmol, yield: 98.8%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 508.4 [M+1]

Step 9

N-ethyl-5-fluoro-2-[6-(1-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylhexan-3-yl}azacyclobutan-3-yl)-3-methylimidazo[1,5-a]pyrazin-8-yl]-*N*-(isopropyl)benzamide **491**

The crude product of Compound **491i** (40 mg, 78.80 μmol) and 2-(piperazin-1-yl)ethanol (15.39 mg, 118.19 μmol) were dissolved in methanol (2 mL). Acetic acid (4.73 mg, 78.80 μmol) was added, and the mixture was stirred at 35°C for 1.0 hour. Sodium cyanoborohydride (14.86 mg, 236.39 μmol) was added, allowing for reacting at 35°C for 11 hours. A saturated aqueous sodium carbonate solution (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (10 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The obtained crude product was purified by the reverse-phase C18 column chromatography (mobile phase: acetonitrile, water, elution gradient: 0%-100%). The title Compound **491** (9.33 mg, 15.00 μmol, yield: 19.04%) was obtained as yellow gel.

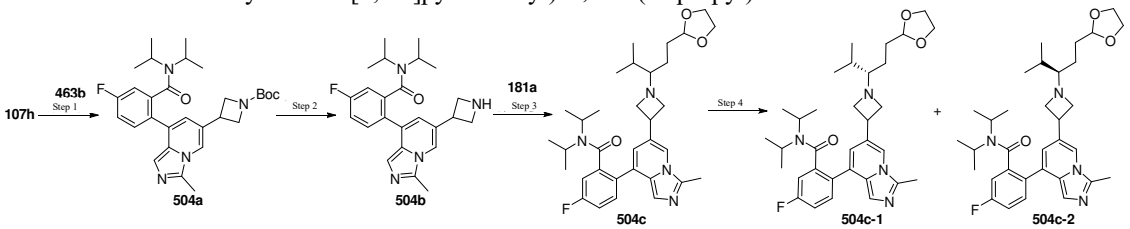
MS m/z (ESI):622.3 [M+1]

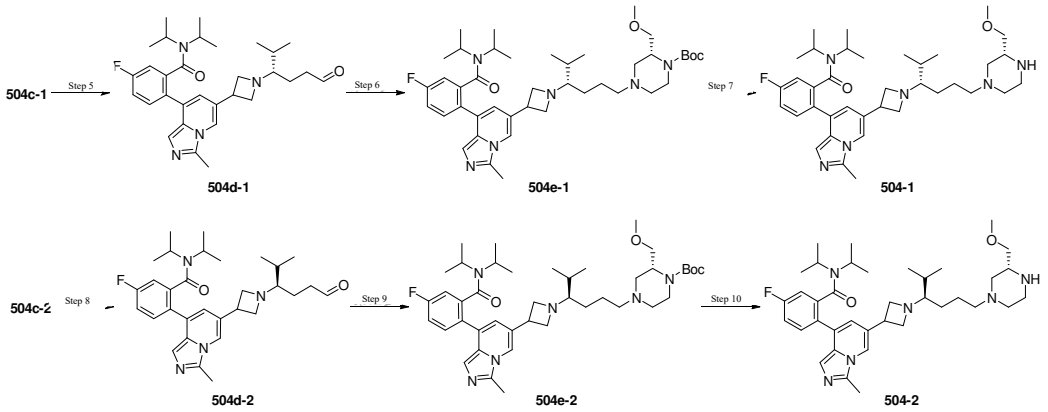
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.65 (br d, J = 4.3 Hz, 1H), 7.52 (s, 1H), 7.27 – 7.07 (m, 2H), 4.64 – 4.46 (m, 2H), 4.22 – 3.78 (m, 4H), 3.73 – 3.58 (m, 3H), 3.21 (m, 1H), 2.98 – 2.78 (m, 1H), 2.69 (s, 3H), 2.53 (m, 7H), 2.34 (m, 2H), 2.17 – 1.81 (m, 8H), 1.45 (m, 1H), 1.33 – 1.22 (m, 2H), 0.93 (m, 11H), 0.70 – 0.40 (m, 2H).

Examples 504-1 and 504-2

5-fluoro-2-(6-{1-[(3*S*)-6-[(3*R*)-3-(methoxymethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504-1**

5-fluoro-2-(6-{1-[(3*R*)-6-[(3*R*)-3-(methoxymethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504-2**





Step 1

3-(8-{2-[di(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-*a*]pyridin-6-yl)azacyclobutan-1-tert-butyl carboxylate **504a**

Compound **107h** (700 mg, 2.18 mmol), Compound **463b**(1.40 g, 2.61 mmol) and potassium phosphate (1.15 g, 5.44 mmol) were dissolved in dioxane (10.0 mL) and water (2.0 mL). Xphos Pd G4 (56.15 mg, 65.26 μmol) was added. Under a nitrogen atmosphere, the mixture was stirred at 90°Cto allow for reacting for 1.0 hours. The reaction mixture was cooled to room temperature, water (15 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative column chromatography using dichloromethane/ethyl acetate as an elution system, to obtain the title Compound **504a** (950 mg, 1.87 mmol, yield: 85.86%).

MS m/z (ESI): 509.4[M+1]

Step 2

2-[6-(azacyclobutan-3-yl)-3-methylimidazo[1,5-*a*]pyridin-8-yl]-5-fluoro-*N,N*-di(isopropyl)benzamide **504b**

Compound **504a** (950 mg, 1.87 mmol) was dissolved in methane dioxide (10.0 mL), followed by the addition of trifluoroacetic acid (4.44 g, 38.94 mmol, 3 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 1.0 hours. The mixture was concentrated under a reduced pressure, followed by the addition of dichloromethane (20 mL), and the mixture was regulated to pH > 7 with a saturated aqueous potassium carbonate solution and extracted with dichloromethane (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **504b** (750 mg, 1.84 mmol, yield: 98.3%). The crude product was directly used in the next step of reaction without purification.

MS m/z (ESI): 409.2 [M+1]

Step 3

2-(6-{1-[1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N,N*-di(isopropyl)benzamide **504c**

Compound **504b** (750 mg, 1.84 mmol) and 1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one **181a** (474.28 mg, 2.75 mmol) were dissolved in methanol (10.0 mL), followed by the addition of acetic acid (220.50 mg, 3.67 mmol), and the mixture was stirred at 50°C for 0.5 hours. The mixture was cooled to room temperature, followed by adding sodium cyanoborohydride (346.12 mg, 5.51 mmol) and stirring at 50°C for 1.5 hour. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the silica-gel column chromatography using ethyl acetate/methanol as an elution system, to obtain the title Compound **504c** (900 mg, 1.59 mmol, yield: 86.80%)

MS m/z (ESI): 565.5 [M+1]

Step 4

2-(6-{1-[(3*S*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N,N*-di(isopropyl)benzamide **504c-1**

2-(6-{1-[(3*R*)-1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-5-fluoro-*N,N*-di(isopropyl)benzamide **504c-2**

Compound **504c** (900 mg, 1.59 mmol) was separated and purified by the chiral preparative SFC (preparative column: DAICEL CHIRALCEL OD (250 mm * 30 mm,10 um), mobile phase: carbon dioxide-isopropanol (0.1% ammonia water); elution gradient: 30%), to obtain the title Compounds **504c-1** (400 mg, 708.30 μmol, yield: 44.4%) and **504c-2** (400 mg, 708.30 μmol, yield: 44.4%).

Single-configuration Compound 504c-1:

MS m/z (ESI):565.5 [M+1]
Chiral HPLC analysis: retention time: 1.383 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.
Single-configuration Compound 504c-2:
MS m/z (ESI):565.4 [M+1]
Chiral HPLC analysis: retention time: 1.664 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-isopropanol (0.05% diethylamide): elution gradient: 5%-40%.

Step 5

5-fluoro-2-(3-methyl-6-{1-[(3*S*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504d-1**

Compound **504c-1** (200 mg, 354.15 μmol) was dissolved in acetonitrile (6.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a 10 % aqueous NaOH solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **504d-1** (184 mg, 353.38 μmol,yield: 99.78%). The crude product was directly used in the next step of reaction without purification.
Single-configuration Compound 504d-1:
MS m/z (ESI): 521.4 [M+1]

Step 6

(2*R*)-4-[(4*S*)-4-[3-(8-{2-[di(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-(methoxymethyl)piperazin-1-tert-butyl carboxylate **504e-1**

The crude product of Compound **504d-1** (184 mg, 353.38 μmol) and (2*R*)-2-(methoxymethyl)piperazin-1-tert-butyl carboxylate (81.39 mg, 353.38 μmol) were dissolved in methanol (5.0 mL), followed by the addition of acetic acid (2.12 mg, 35.34 μmol), and the mixture was stirred at 40°C for 1.0 hour. Sodium cyanoborohydride (66.62 mg, 1.06 mmol) was added, allowing for reacting 40°C for 12.0 hours under the protection of nitrogen. A saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **504e-1** (259 mg, 352.39 μmol, yield: 99.72%). The crude product was directly used in the next step of reaction without purification.
Single-configuration Compound 504e-1:
MS m/z (ESI):735.4 [M+1]

Step 7

5-fluoro-2-(6-{1-[(3*S*)-6-[(3*R*)-3-(methoxymethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504-1**

Compound **504e-1** (259 mg, 352.39 μmol) was dissolved in dichloromethane (3.0 mL), followed by the addition of trifluoroacetic acid (1.48 g, 12.98 mmol, 1 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 2.0 hours. The reaction mixture was concentrated under a reduced pressure, dissolved by adding dichloromethane (20 mL), regulated to PH = 10 with a 10% aqueous sodium hydroxide solution, and extracted with dichloromethane/isopropanol (10/1, 20 mL x 5), and the organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **504-1** (46.44 mg, 73.15 μmol, yield: 20.76%).
MS m/z (ESI): 635.3 [M+1]
Chiral HPLC analysis: retention time: 1.128 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 4.4 Hz, 1H), 7.66 (dd, J = 5.6, 8.8 Hz, 1H), 7.35 (dt, J = 2.8, 8.8 Hz, 1H), 7.23 (dd, J = 2.8, 8.9 Hz, 1H), 7.01 (s, 1H), 6.84 – 6.71 (m, 1H), 4.49 – 3.35 (m, 6H), 3.30 – 2.96 (m, 9H), 2.80 – 2.61 (m, 4H), 2.58 (d, J = 1.2 Hz, 3H), 2.23 – 2.14 (m, 2H), 2.04 – 1.97 (m, 1H), 1.87 – 1.79 (m, 1H), 1.74 – 1.65 (m, 1H), 1.62 – 1.53 (m, 1H), 1.49 – 1.34 (m, 5H), 1.28 – 1.04 (m, 6H), 0.92 – 0.89 (m, 2H), 0.87 – 0.79 (m, 6H), 0.22 (br d, J = 6.4 Hz, 2H).

Step 8

5-fluoro-2-(3-methyl-6-{1-[(3*R*)-2-methyl-6-oxohexan-3-yl]azacyclobutan-3-yl}imidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504d-2**

Compound **504c-2** (200 mg, 354.15 μmol) was dissolved in acetonitrile (2.0 mL), followed by the addition of a hydrochloric acid solution (1.0 M; 2.0 mL). The mixture was stirred at 50°C to allow for reacting for 1.0 hours. The reaction mixture was concentrated under a reduced pressure, regulated to pH = 10 with a saturated aqueous potassium

carbonate solution, and extracted with dichloromethane (15 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **504d-2** (180 mg, 345.70 μmol,yield: 97.61%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 504d-2:

MS m/z (ESI): 521.3 [M+1]

Step 9

(2*R*)-4-[(4*R*)-4-[3-(8-{2-[di(isopropyl)aminoformyl]-4-fluorophenyl}-3-methylimidazo[1,5-a]pyridin-6-yl)azacyclobutan-1-yl]-5-methylhexyl]-2-(methoxymethyl)piperazin-1-tert-butyl carboxylate **504e-2**

The crude product of Compound **504d-2** (200 mg, 384.11 μmol) and (2*R*)-2-(methoxymethyl)piperazin-1-tert-butyl carboxylate (97.31 mg, 422.52 μmol) were dissolved in methanol (3.0 mL), followed by the addition of acetic acid (34.60 mg, 576.17 μmol), and the mixture was stirred at 50℃ for 0.5 hour. Sodium cyanoborohydride (72.42 mg, 1.15 mmol) was added, allowing for reacting 50℃ for 12.0 hours under the protection of nitrogen. Ethyl acetate (20 mL) was added to the reaction mixture, which was then washed with water (20 mL x 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure, to obtain the crude product of title Compound **504e-2** (200 mg, 272.12 μmol, yield: 70.84%). The crude product was directly used in the next step of reaction without purification.

Single-configuration Compound 504e-2:

MS m/z (ESI):735.5 [M+1]

Step 10

5-fluoro-2-(6-{1-[(3*R*)-6-[(3*R*)-3-(methoxymethyl)piperazin-1-yl]-2-methylhexan-3-yl]azacyclobutan-3-yl}-3-methylimidazo[1,5-a]pyridin-8-yl)-*N,N*-di(isopropyl)benzamide **504-2**

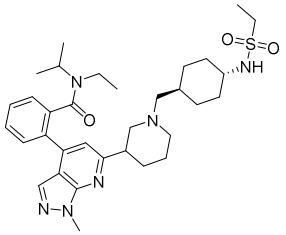
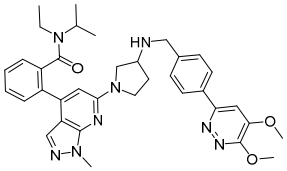
Compound **504e-2** (200 mg, 272.12 μmol) was dissolved in dichloromethane (2.0 mL), followed by the addition of trifluoroacetic acid (740.00 mg, 6.49 mmol, 0.5 mL) at 0°C. The mixture was stirred at room temperature to allow for reacting for 0.5 hours. The reaction mixture was concentrated under a reduced pressure, followed by adding a saturated aqueous sodium bicarbonate solution (30 mL) and extracting with dichloromethane (30 mL x 3), and the organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. The resulting residues were purified by the preparative thin-layer chromatography using dichloromethane/methanol as an elution system, to obtain the title Compound **504-2** (58.29 mg, 91.81 μmol, yield: 33.74%) as yellow solid.

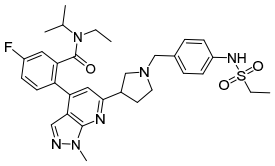
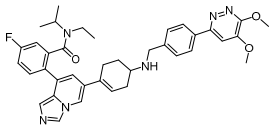
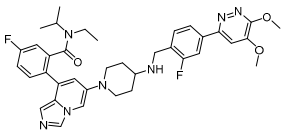
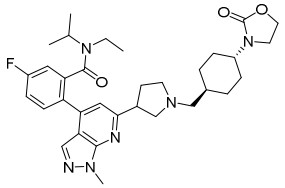
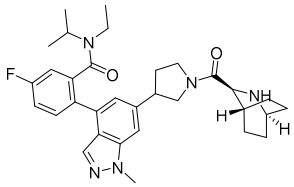
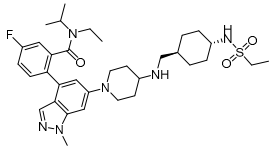
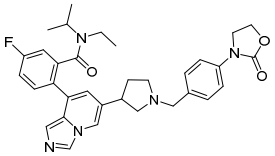
MS m/z (ESI): 635.5 [M+1]

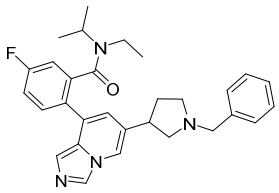
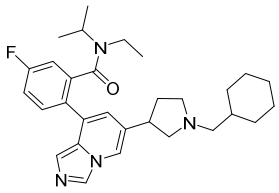
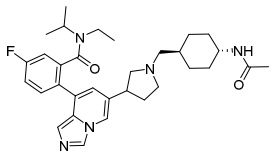
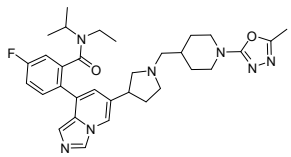
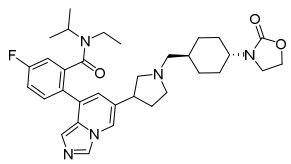
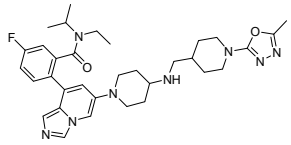
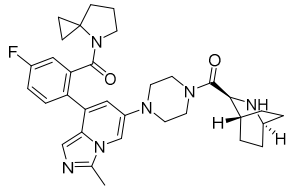
Chiral HPLC analysis: retention time: 1.185 min; chromatographic column: Chiralcel OD-3 50 x 4.6 mm I.D., 3 um; mobile phase: carbon dioxide-methanol (0.05% diethylamide): elution gradient: 5%-40%.

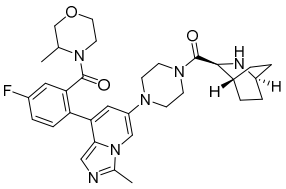
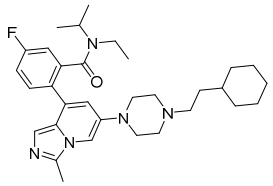
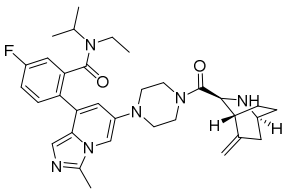
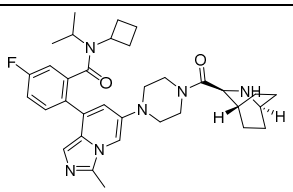
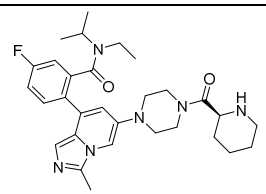
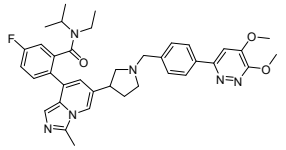
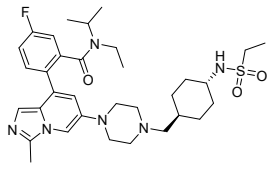
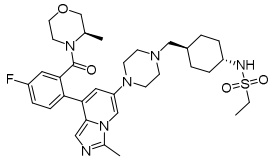
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 3.6 Hz, 1H), 7.66 (dd, J = 5.6, 8.4 Hz, 1H), 7.35 (dt, J = 2.4, 8.8 Hz, 1H), 7.23 (dd, J = 2.8, 8.8 Hz, 1H), 7.02 (s, 1H), 6.83 – 6.73 (m, 1H), 3.61 – 3.41 (m, 5H), 3.28 – 3.19 (m, 7H), 3.09 – 3.01 (m, 1H), 2.88 – 2.77 (m, 2H), 2.72 – 2.62 (m, 3H), 2.59 (s, 3H), 2.25 – 2.15 (m, 2H), 2.04 – 1.98 (m, 1H), 1.94 – 1.84 (m, 1H), 1.74 – 1.59 (m, 2H), 1.49 – 1.39 (m, 2H), 1.37 (d, J = 6.8 Hz, 3H), 1.23 – 1.13 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.87 – 0.80 (m, 6H), 0.22 (d, J = 6.4 Hz, 3H).

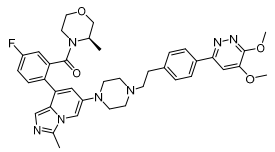
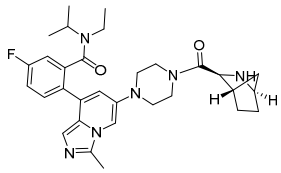
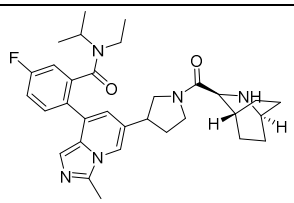
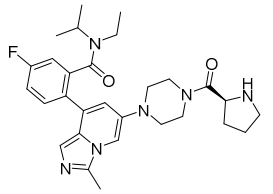
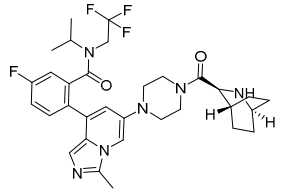
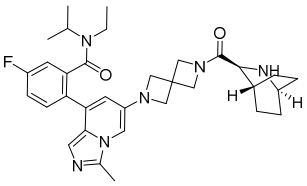
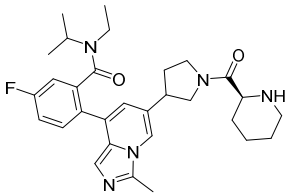
The following compounds were prepared and characterized according to the general synthetic scheme described herein and similar steps to those in the aforementioned embodiments.

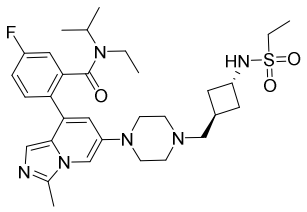
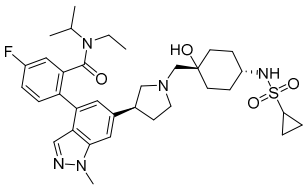
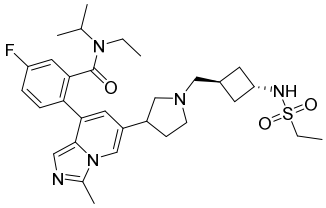
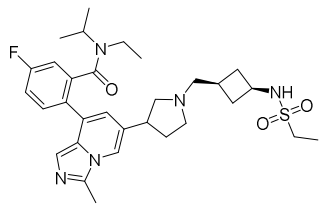
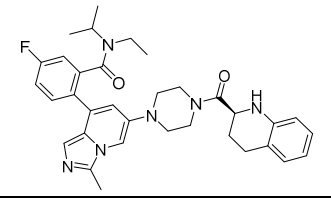
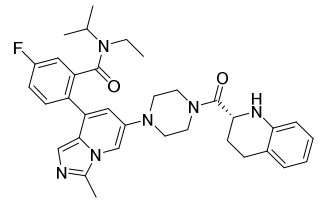
Example	Structure	MS m/z (ESI) $[M+H]^+$	H NMR Spectroscopy
7		609.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 134.4 Hz, 1H), 8.03 (s, 1H), 7.62 (m, 3H), 7.47 (m, 1H), 7.21 (m, 1H), 7.07 (dd, *J* = 10.8, 6.1 Hz, 1H), 4.10 (d, *J* = 25.6 Hz, 3H), 3.65 (dd, *J* = 55.2, 14.0 Hz, 2H), 3.01 (m, 9H), 1.93 (m, 10H), 0.98 (m, 15H), 0.20 (t, *J* = 6.8 Hz, 2H).
10		635.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.71 – 7.37 (m, 8H), 6.47 – 6.39 (m, 1H), 4.36 – 4.27 (m, 0.31H), 4.11 – 3.91 (m, 7.69H), 3.90 – 3.82 (m, 3H), 3.79 – 3.37 (m, 6H), 2.98 – 2.69 (m, 1H), 2.30 – 1.95 (m, 3H), 1.15 – 0.58 (m, 7H), 0.27 (d, *J* = 6.8 Hz, 2H).

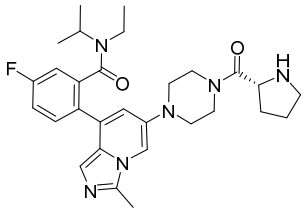
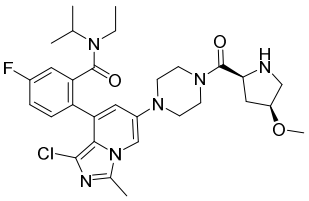
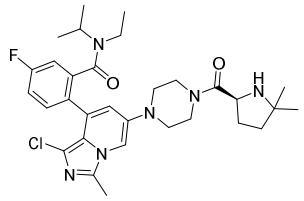
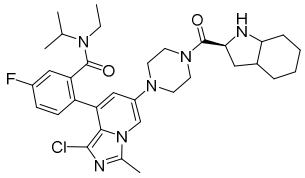
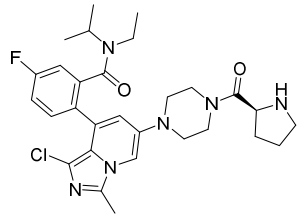
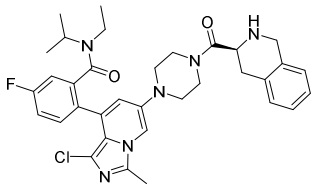
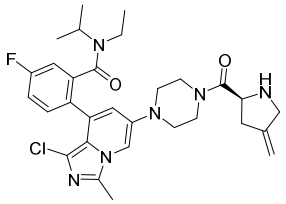
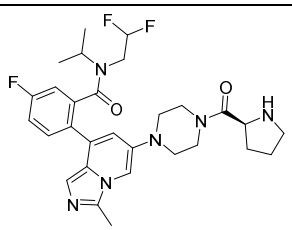
12		607.2	^{1}H NMR (400 MHz, DMSO-d_6-D_2O) δ 7.95 (d, *J* = 2.4 Hz, 1H), 7.73 – 7.61 (m, 1H), 7.45 (td, *J* = 8.4, 2.4 Hz, 1H), 7.41 – 7.25 (m, 3H), 7.21 – 7.07 (m, 3H), 4.21 – 4.14 (m, 0.24H), 4.04 (s, 3H), 3.63 (s, 3H), 3.40 – 3.19 (m, 2H), 3.05 (d, *J* = 7.2 Hz, 3H), 2.92 – 2.81 (m, 1H), 2.76 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.69 (t, *J* = 9.6 Hz, 2H), 2.26 (s, 1H), 2.13 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.0 Hz, 3H), 0.79 – 0.59 (m, 3H), 0.16 (s, 2H).
17		649.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 7.2 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.75 – 7.67 (m, 1H), 7.60 – 7.56 (m, 1H), 7.53 – 7.48 (m, 2H), 7.42 -7.30 (m, 2H), 7.17 – 7.11 (m, 1H), 6.92 – 6.86 (m, 1H), 6.10 (s, 1H), 4.07 – 4.03 (m, 3H), 3.98 (s, 3H), 3.85 (s, 2H), 3.46 – 3.38 (m, 2H), 2.90 – 2.63 (m, 3H),2.48 – 2.43 (m, 2H), 2.33 (s, 1H), 2.09 – 1.93 (m, 2H), 1.55 – 1.42 (m, 1H), 1.06 – 0.78 (m, 4H), 0.76 – 0.67 (m, 3H), 0.24 (d, J = 6.4 Hz, 2H).
20		670.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.98 – 7.87 (m, 2H), 7.78 (s, 1H), 7.71 – 7.61 (m, 3H), 7.41 – 7.28 (m, 2H), 7.07 – 7.02 (m, 1H), 6.68 – 6.61 (m, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 3.86 (s, 2H), 3.49 – 3.39 (m, 3H), 2.99 – 2.86 (m, 1H), 2.84 – 2.55 (m, 4H), 2.01 – 1.90 (m, 2H), 1.52 – 1.38 (m, 2H), 0.93 – 0.71 (m, 7H), 0.33 – 0.29 (m, 2H).
28		591.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.73 – 7.61 (m, 1H), 7.49 – 7.34 (m, 2H), 7.13 (s, 1H), 4.27 – 4.19 (m, 2H), 4.04 (s, 3H), 3.59 – 3.53 (m, 1H), 3.47 (m, 2H), 3.40 – 3.35 (m, 2H), 3.07 – 2.57 (m, 6H), 2.41 – 1.13 (m, 12H), 1.05 – 0.59 (m, 8H), 0.21 (dd, J = 6.0, 3.6 Hz, 2H).
32		546.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.90 – 7.74 (m, 1H), 7.64 – 7.50 (m, 2H), 7.38 (t, J = 8.4 Hz, 1H), 7.28 (t, J = 10.4 Hz, 1H), 7.11 – 6.95 (m, 1H), 4.30 – 3.94 (m, 5H), 3.94 – 3.74 (m, 1H), 3.71 – 3.57 (m, 2H), 3.43 – 3.31 (m, 2H), 3.23 (dd, J = 25.6, 11.2 Hz, 2H), 2.89 – 2.75 (m, 1H), 2.30 (d, J = 21.6 Hz, 1H), 2.08 (d, J = 18.8 Hz, 2H), 1.78 (d, J = 18.4 Hz, 3H), 1.63 (d, J = 7.2 Hz, 2H), 1.57 – 1.37 (m, 3H), 1.05 – 0.54 (m, 7H), 0.05 (d, J = 6.4 Hz, 2H).
37		641.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1.73H), 7.70 (s, 1H), 7.62 – 7.56 (m, 1H), 7.38 (td, J = 8.8, 2.8 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.88 (d, J = 2.0 Hz, 1H), 3.97 (s, 3H), 3.87 (d, J = 12.0 Hz, 2H), 3.40 – 3.20 (m, 2H), 3.09 – 2.95 (m, 3H), 2.88 – 2.75 (m, 4H), 2.48 – 2.37 (m, 2H), 2.09 (d, J = 11.6 Hz, 2H), 1.91 (d, J = 10.4 Hz, 2H), 1.79 (d, J = 11.6 Hz, 2H), 1.67 – 1.48 (m, 3H), 1.28 –1.15 (s, 5H), 1.05 (q, J = 12.4 Hz, 2.7H), 0.87 (d, J = 6.8 Hz, 2.6H), 0.75 (t, J = 7.2 Hz, 2.8H), 0.65 (t, J = 7.2 Hz, 0.6H), 0.13 (t, J = 7.6 Hz, 2.2H).
41		570.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.26 – 8.12 (m, 2H), 7.71 – 7.62 (m, 1H), 7.54 – 7.46 (m, 2H), 7.42 – 7.29 (m, 4H), 7.11 (s, 1H), 6.75 – 6.65 (m, 1H), 4.48 – 4.39 (m, 3H), 4.07 – 4.00 (m, 3H), 3.67 – 3.58 (m, 2H), 3.49 – 3.37 (m, 1H), 3.29 – 3.23 (m, 1H), 2.96 – 2.83 (m, 2H), 2.74 – 2.64 (m, 2H), 2.28 – 2.12 (m, 1H), 1.90 – 1.71 (m, 1H), 1.07 – 0.68 (m, 7H), 0.31 – 0.19 (m, 2H).

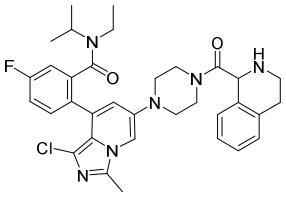
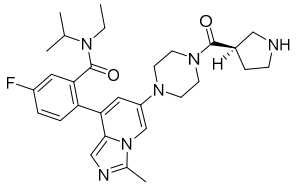
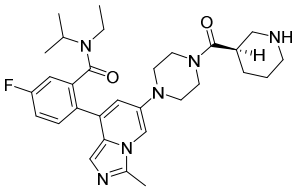
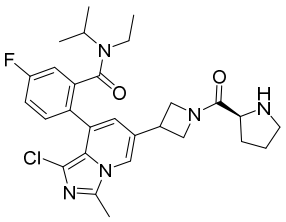
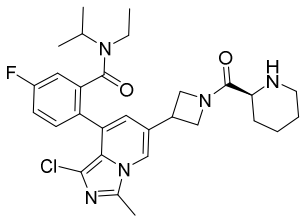
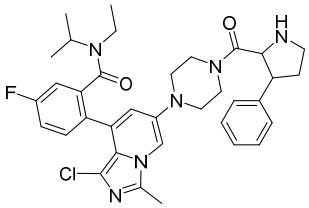
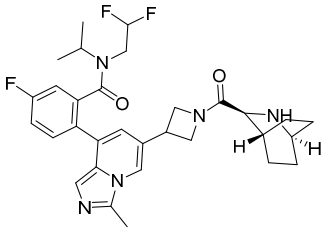
43		485.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 3.6 Hz, 1H), 7.84 (m, J = 4.8 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.43 (br s, 1H), 7.38 (br s, 1H), 7.34 (m, J = 8.8 Hz, 1H), 7.30 (m, J = 9.2 Hz, 1H), 7.25 (s, 1H), 7.24 – 7.16 (m, 2H), 7.14 (m, J = 11.2 Hz, 1H), 6.83 (m, J = 4.0 Hz, 1H), 3.77 (m, J = 2.96 Hz, 2H), 3.44 – 3.28 (m, 2H), 3.03 – 2.94 (m, 2H), 2.89 – 2.77 (m, 1H), 2.73 – 2.49 (m, 1H), 2.41 – 2.27 (m, 1H), 2.05 – 1.85 (m, 1H), 1.27 (br s, 1H), 0.98 – 0.91 (m, 5H), 0.78 (br t, J = 2.2 Hz, 2H), 0.24 (t, J = 3.6 Hz, 3H).
44		491.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.93 – 7.73 (m, 1H), 7.62 – 7.55 (m, 1H), 7.17 – 7.09 (m, 2H), 7.08 – 7.02 (m, 1H), 6.76 – 6.68 (m, 1H), 3.43 (m, J = 2.56 Hz, 2H), 3.36 – 3.26 (m, 1H), 3.00 – 2.86 (m, 2H), 2.84 – 2.76 (m, 1H), 2.68 – 2.59 (m, 1H), 2.46 – 2.35 (m, 1H), 1.96 – 1.79 (m, 3H), 1.73 – 1.65 (m, 3H), 1.64 – 1.58 (m, 3H), 1.22 – 1.17 (m, 2H), 1.16 – 1.13 (m, 1H), 1.09 – 1.05 (m, 1H), 0.93 – 0.84 (m, 7H), 0.73 – 0.68 (m, 1H), 0.19 (d, J = 6.8 Hz, 3H).
45		548.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.26 – 8.20 (m, 1H), 7.73 – 7.62 (m, 2H), 7.39 (q, J = 8.4 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.13 – 7.09 (m, 1H), 6.72 – 6.65 (m, 1H), 3.56 – 3.35 (m, 6H), 3.31 – 3.16 (m, 2H), 3.01 – 2.76 (m, 2H), 2.71 – 2.63 (m, 1H), 2.62 – 2.53 (m, 2H), 2.43 – 2.31 (m, 1H), 2.27 – 2.13 (m, 2H), 1.83 – 1.78 (m, J = 4.4 Hz, 2H), 1.57 – 1.43 (m, 1H), 1.40 – 1.30 (m, 1H), 1.27 – 1.02 (m, 3H), 0.90 (d, J = 5.6 Hz, 5H), 0.80 – 0.73 (m, 3H), 0.28 (br dd, J = 6.8, 7.2 Hz, 2H).
46		574.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.27 – 8.20 (m, 1H), 8.16 (s, 0.3H), 7.72 – 7.62 (m, 1H), 7.43 – 7.27 (m, 2H), 7.15 – 7.07 (m, 1H), 6.75 – 6.66 (m, 1H), 3.81 – 3.74 (m, 2H), 3.47 – 3.40 (m, 1H), 3.33 – 3.21 (m, 2H), 2.99 – 2.81 (m, 4H), 2.76 – 2.54 (m, 3H), 2.41 – 2.29 (m, 5H), 2.23 – 2.13 (m, 1H), 1.93 – 1.66 (m, 4H), 1.20 – 1.08 (m, 2H), 0.96 – 0.68 (m, 7H), 0.30 – 0.23 (m, 2H).
47		576.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.28 – 8.22 (m, 1H), 8.19 (s, 1H), 7.71 – 7.62 (m, 1H), 7.43 – 7.27 (m, 2H), 7.12 (s, 1H), 6.74 – 6.66 (m, 1H), 4.27 – 4.18 (m, 2H), 3.56 – 3.20 (m, 6H), 3.11 – 2.70 (m, 4H), 2.67 – 2.54 (m, 1H), 2.45 – 2.38 (m, 1H), 2.26 – 2.13 (m, 1H), 1.98 – 0.68 (m, 18H), 0.34 – 0.21 (m, 2H).
49		603.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.68 – 7.60 (m, 1H), 7.30 (s, 1H), 7.21 – 7.11 (m, 3H), 6.85 – 6.78 (m, 1H), 4.03 – 3.94 (m, 3H), 3.59 – 3.41 (m, 4H), 3.04 – 2.89 (m, 4H), 2.75 – 2.55 (m, 7H), 2.27 – 2.18 (m, 1H), 2.07 – 1.95 (m, 4H), 1.02 – 0.76 (m, 10H), 0.33 – 0.24 (m, 3H).
63		571.5	^{1}H NMR (400 MHz, METHANOL-d4) δ 7.74 – 7.69 (m, 1H), 7.38 – 7.33 (m, 3H), 7.15 (s, 1H), 6.80 – 6.76 (m, 1H), 4.56 – 4.54 (m, 1H), 3.74 – 3.66 (m, 3H), 3.61 – 3.46 (m, 3H), 3.24 – 3.21 (m, 4H), 2.71 – 2.67 (m, 4H), 2.23 – 2.16 (m, 3H), 1.88 – 1.84 (m, 2H), 1.63 – 1.59 (m, 3H), 1.34 – 1.32 (m, 6H), 0.92 – 0.89 (m, 3H).

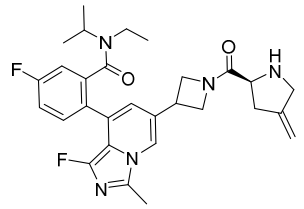
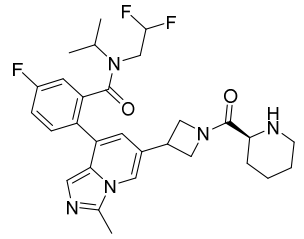
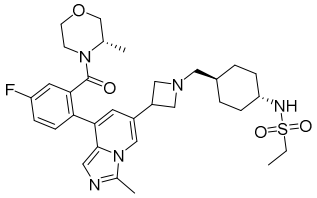
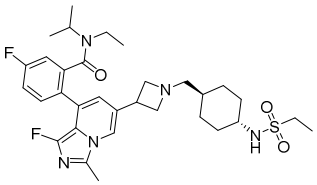
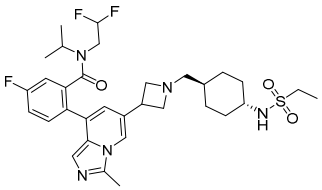
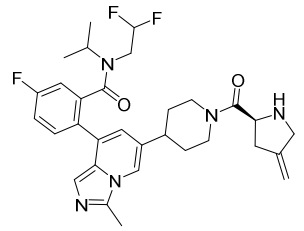
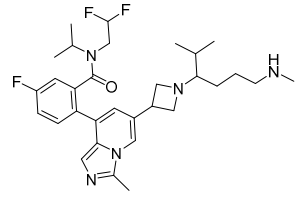
64		575.2	^{1}H NMR (400 MHz, DMSO-d6) δ = 7.86 – 7.58 (m, 1H), 7.51 – 7.26 (m, 3H), 7.09 – 6.88 (m, 1H), 6.71 – 6.44 (m, 1H), 4.63 – 4.00 (m, 1H), 3.99 – 3.86 (m, 1H), 3.80 – 3.42 (m, 6H), 3.25 – 2.72 (m, 9H), 2.62 – 2.54 (m, 3H), 1.93 – 1.42 (m, 9H), 1.21 – 0.99 (m, 2H), 0.76 – 0.37 (m, 1H).
66		534.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.63 (m, 1H), 7.42 – 7.23 (m, 3H), 7.01 – 6.94 (m, 1H), 6.64 – 6.58 (m, 1H), 3.48 – 3.39 (m, 2H), 3.06 – 2.86 (m, 5H), 2.57 – 2.52 (m, 3H), 2.49 (br s, 4H), 2.38 – 2.30 (m, 2H), 1.73 – 1.57 (m, 5H), 1.37 – 1.10 (m, 7H), 0.96 – 0.79 (m, 8H), 0.31 (br d, J = 6.5 Hz, 2H).
74		573.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.61 (m, 1H), 7.40 – 7.29 (m, 2H), 7.00 – 6.96 (m, 1H), 6.62 (br d, J = 1.3 Hz, 1H), 6.44 – 6.32 (m, 1H), 4.97 – 4.93 (m, 1H), 4.76 – 4.69 (m, 1H), 4.36 (s, 1H), 3.94 (s, 1H), 3.77 – 3.57 (m, 2H), 3.47 – 3.40 (m, 1H), 3.19 – 3.12 (m, 2H), 3.02 (br s, 4H), 2.55 (s, 2H), 2.38 (br s, 1H), 2.34 – 2.19 (m, 2H), 2.15 (s, 1H), 2.08 (s, 1H), 1.72 – 1.51 (m, 3H), 1.49 – 1.39 (m, 2H), 1.35 – 1.27 (m, 1H), 1.09 (t, J = 7.2 Hz, 1H), 0.96 – 0.88 (m, 3H), 0.84 – 0.73 (m, 3H), 0.33 – 0.28 (m, 2H).
78		587.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.64 (m, 1H), 7.41 – 7.13 (m, 3H), 7.03 – 6.97 (m, 1H), 6.70 – 6.49 (m, 1H), 3.96 (s, 1H), 3.86 – 3.74 (m, 1H), 3.69 – 3.50 (m, 5H), 3.07 – 2.93 (m, 4H), 2.86 (s, 1H), 2.55 (s, 3H), 2.06 – 1.32 (m, 17H), 1.14 – 1.08 (m, 2H), 0.94 – 0.85 (m, 1H), 0.34 – 0.24 (m, 1H).
81		535.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.75 – 7.68 (m, 1H), 7.38 – 7.30 (m, 2H), 7.28 – 7.21 (m, 1H), 7.09 (s, 1H), 6.81 – 6.76 (m, 1H), 4.21 – 4.09 (m, 1H), 3.87 – 3.66 (m, 4H), 3.61 – 3.41 (m, 2H), 3.22 – 2.87 (m, 7H), 2.62 (s, 3H), 1.97 – 1.52 (m, 6H), 1.10 – 0.76 (m, 7H), 0.35 – 0.31 (m, 2H).
83		637.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.65 (m, 3H), 7.47 – 7.03 (m, 6H), 6.80 – 6.73 (m, 1H), 6.50 – 6.42 (m, 1H), 3.89 – 3.77 (m, 3H), 3.74 (s, 3H), 3.53 – 3.35 (m, 2H), 3.27 – 3.14 (m, 1H), 3.06 – 2.94 (m, 2H), 2.78 – 2.59 (m, 2H), 2.53 – 2.41 (m, 2H), 2.34 (s, 3H), 2.04 – 1.90 (m, 1H), 1.69 – 1.52 (m, 1H), 1.06 – 0.41 (m, 8H), 0.10 - -0.05 (m, 2H).
84		627.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.62 (m, 1H), 7.40 – 7.22 (m, 3H), 7.03 – 6.95 (m, 2H), 6.65 – 6.57 (m, 1H), 3.48 – 3.38 (m, 1H), 3.24 – 3.15 (m, 1H), 3.04 – 2.90 (m, 8H), 2.58 – 2.52 (m, 3H), 2.45 (s, 3H), 2.15 – 2.07 (m, 2H), 1.92 – 1.72 (m, 5H), 1.49 – 1.34 (m, 1H), 1.22 – 1.15 (m, 5H), 0.98 – 0.71 (m, 9H), 0.33 – 0.29 (m, 2H).
85		641.3	^{1}H NMR (400 MHz,$CDCl_3$) δ 7.72 – 7.61 (m, 1H), 7.24 – 7.19 (m, 1H), 7.19 – 7.12 (m, 1H), 7.12 – 7.09 (m, 1H), 7.02 – 6.93 (m, 1H), 6.76 (s, 1H), 6.66 – 6.63 (m, 1H), 4.69 – 4.43 (m, 1H), 4.21 – 3.72 (m, 1H), 3.63 – 3.51 (m, 1H), 3.37 – 3.31 (m, 2H), 3.27 – 3.21 (m, 1H), 3.17 – 3.13 (m, J = 4.8 Hz, 1H), 3.05 (q, J = 7.4 Hz, 3H), 2.91 – 2.76 (m, 1H), 2.64 (s, 3H), 2.56 – 2.54 (m, J = 8.4 Hz, 2H), 2.19 (d, J = 7.2 Hz, 2H), 2.13 – 2.07 (m, J = 10.0 Hz, 2H), 1.90 (d, J = 11.6 Hz, 2H), 1.71 – 1.63 (m, 2H), 1.50 – 1.43 (m, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.31 – 1.26 (m, 2H), 1.25 – 1.20

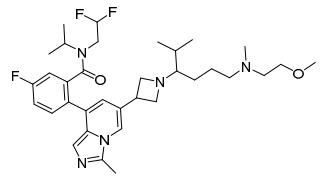
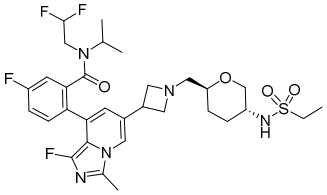
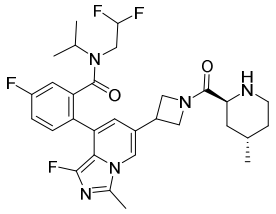
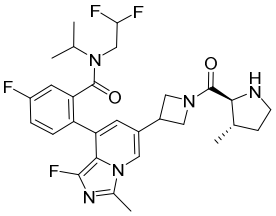
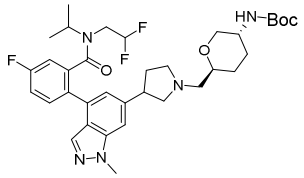
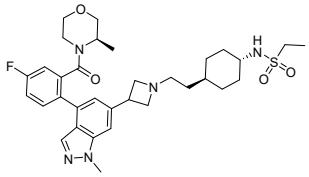
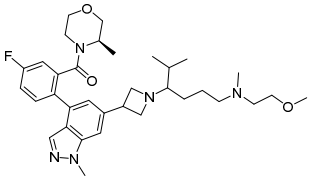
			(m, 1H), 1.10 (d, J = 6.8 Hz, 1H), 1.02 (t, J = 7.2 Hz, 3H), 0.86 (d, J = 6.8 Hz, 1H).
86		680.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.75 – 7.64 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.25 – 7.17 (m, 2H), 7.15 (s, 2H), 7.05 – 6.98 (m, 1H), 6.82 – 6.63 (m, 1H), 4.25 (s, 3H), 4.04 (s, 3H), 3.82 – 3.72 (m, 1H), 3.68 – 3.51 (m, 2H), 3.35 – 3.05 (m, 6H), 3.03 – 2.92 (m, 3H), 2.91 – 2.73 (m, 6H), 2.67 (s, 3H), 1.41 – 1.25 (m, 2H), 1.12 (d, J = 6.4 Hz, 1H), 0.93 – 0.84 (m, 1H).
88		547.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 5.2, 8.4 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.24 (dd, J = 2.8, 8.8 Hz, 1H), 7.09 (s, 1H), 6.81 – 6.78 (m, 1H), 3.92 – 3.81 (m, 3H), 3.78 – 3.67 (m, 3H), 3.56 (td, J = 6.8, 13.6 Hz, 1H), 3.45 (td, J = 6.4, 13.2 Hz, 1H), 3.28 – 3.09 (m, 4H), 3.08 – 2.98 (m, 1H), 2.70 (s, 1H), 2.62 (s, 3H), 1.82 – 1.72 (m, 2H), 1.71 – 1.62 (m, 2H), 1.61 – 1.54 (m, 1H), 1.52 – 1.46 (m, 1H), 1.21 – 1.06 (m, 1H), 1.03 – 0.90 (m, 6H), 0.81 (t, J = 7.0 Hz, 1H), 0.33 (d, J = 6.8 Hz, 2H).
91		546.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 – 7.90 (m, 1H), 7.72 – 7.61 (m, 1H), 7.42 – 7.28 (m, 2H), 7.04 (s, 1H), 6.70 – 6.53 (m, 1H), 4.00 – 3.54 (m, 4H), 3.53 – 3.38 (m, 3H), 2.99 – 2.86 (m, 1H), 2.79 (s, 1H), 2.59 (s, 3H), 2.34 – 1.22 (m, 12H), 1.08 – 0.70 (m, 7H), 0.32 – 0.23 (m, 2H).
92		521.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.63 (m, 1H), 7.41 – 7.28 (m, 3H), 7.00 – 6.95 (m, 1H), 6.65 – 6.60 (m, 1H), 3.92 – 3.82 (m, 1H), 3.72 – 3.39 (m, 6H), 3.13 – 2.76 (m, 7H), 2.69 – 2.60 (m, 1H), 2.55 (s, 3H), 2.05 – 1.95 (m, 1H), 1.71 – 1.51 (m, 3H), 1.08 – 0.73 (m, 7H), 0.31 (br d, J = 5.2 Hz, 2H).
95		615.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.76 – 7.65 (m, 1H), 7.43 – 7.35 (m, 1H), 7.34 (s, 1H), 7.29 (dd, J = 2.4, 2.8 Hz, 1H), 7.11 – 7.01 (m, 1H), 6.79 – 6.67 (m, 1H), 4.31 – 4.14 (m, 1H), 4.08 (s, 1H), 3.93 – 3.84 (m, 1H), 3.84 – 3.70 (m, 3H), 3.67 (s, 2H), 3.19 – 3.09 (m, 4H), 3.08 – 3.02 (m, 1H), 2.63 (s, 3H), 1.97 – 1.82 (m, 4H), 1.80 – 1.72 (m, 2H), 1.67 – 1.56 (m, 3H), 1.17 – 1.06 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H), 0.45 (d, J = 6.4 Hz, 2H).
96		573.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.62 (m, 1H), 7.40 – 7.28 (m, 2H), 7.05 – 6.94 (m, 2H), 6.27 – 6.18 (m, 1H), 4.46 – 4.26 (m, 2H), 4.15 – 4.02 (m, 2H), 3.95 – 3.88 (m, 4H), 3.55 (s, 1H), 3.47 – 3.39 (m, 1H), 3.31 – 3.29 (m, 1H), 2.99 – 2.88 (m, 1H), 2.78 – 2.74 (m, 1H), 2.52 – 2.51 (m, 3H), 1.76 – 1.66 (m, 3H), 1.60 – 1.37 (m, 6H), 0.94 – 0.72 (m, 7H), 0.33 – 0.27 (m, 2H).
97		520.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 1H), 7.60 – 7.45 (m, 1H), 7.23 – 7.16 (m, 2H), 7.15 – 7.09 (m, 1H), 6.81 – 6.73 (m, 1H), 4.11 – 3.78 (m, 2H), 3.77 – 3.61 (m, 1H), 3.60 – 3.20 (m, 6H), 3.20 – 3.11 (m, 1H), 3.10 – 2.86 (m, 1H), 2.74 – 2.58 (m, 4H), 2.48 – 2.33 (m, 1H), 2.32 – 2.17 (m, 1H), 2.16 – 2.00 (m, 1H), 1.94 (s, 1H), 1.87 – 1.77 (m, 1H), 1.64 – 1.57 (m, 1H), 1.56 – 1.45 (m, 2H), 1.45 – 1.21 (m, 1H), 1.20 – 1.06 (m, 1H), 1.03 – 0.96 (m, 2H), 0.96 – 0.91 (m, 2H), 0.83 – 0.75 (m, 1H), 0.32 – 0.22 (m,

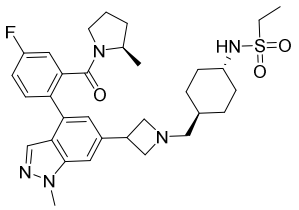
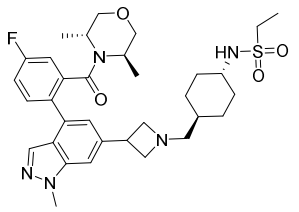
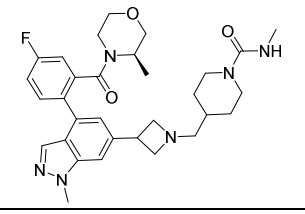
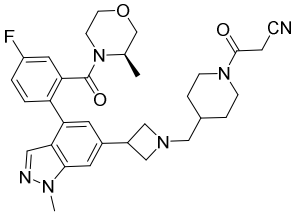
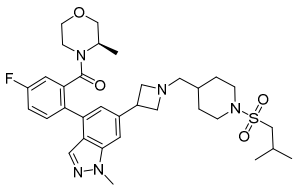
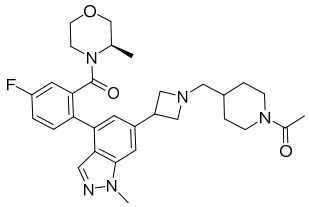
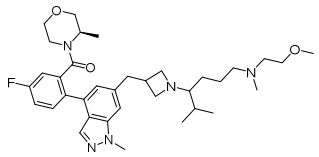
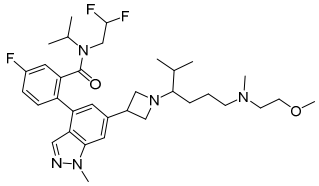
			2H).
99		599.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.54 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.25 – 7.19 (m, 1H), 7.18 (s, 1H), 6.92 – 6.84 (m, 1H), 6.55 – 6.48 (m, 1H), 3.85 – 3.68 (m, 1H), 3.41 – 3.31 (m, 1H), 3.11 – 3.04 (m, 1H), 2.99 – 2.88 (m, 4H), 2.82 (q, J = 7.4 Hz, 3H), 2.46 (s, 4H), 2.36 – 2.32 (m, 2H), 2.02 – 1.93 (m, 4H), 1.59 – 1.40 (m, 1H), 1.29 – 1.14 (m, 1H), 1.09 (t, J = 7.4 Hz, 3H), 0.89 – 0.77 (m, 5H), 0.74 (t, J = 6.8 Hz, 3H), 0.70 – 0.62 (m, 1H), 0.22 (t, J = 8.6 Hz, 2H).
100		640.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 0.86H), 7.79 (s, 1H), 7.62 – 7.51 (m, 2H), 7.38 (td, J = 8.8, 2.4 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.07 (d, J = 15.6 Hz, 1H), 7.03 – 6.90 (m, 1H), 4.20 (dd, J = 13.2, 6.8 Hz, 0.41H), 4.02 (d, J = 3.2 Hz, 3H), 3.42 – 3.18 (m, 4H), 3.14 – 2.63 (m, 7H), 2.45 (t, J = 10.8 Hz, 1H), 2.22 (dd, J = 8.4, 4.0 Hz, 1H), 1.85 (dt, J = 20.0, 7.6 Hz, 1H), 1.70 – 1.19 (m, 8H), 1.06 – 0.53 (m, 11H), 0.08 (t, J = 6.4 Hz, 2H).
102		584.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.96 – 7.86 (m, 1H), 7.76 – 7.64 (m, 1H), 7.40 – 7.30 (m, 1H), 7.29 – 7.19 (m, 1H), 7.13 (s, 1H), 6.86 – 6.78 (m, 1H), 3.67 – 3.48 (m, 1H), 3.45 – 3.35 (m, 2H), 3.29 – 3.23 (m, 2H), 3.13 – 3.03 (m, 2H), 3.03 – 2.95 (m, 2H), 2.94 – 2.85 (m, 1H), 2.77 – 2.69 (m, 2H), 2.67 (s, 3H), 2.64 – 2.55 (m, 1H), 2.54 – 2.40 (m, 2H), 2.38 – 2.28 (m, 1H), 2.26 – 2.16 (m, 4H), 2.03 – 1.84 (m, 1H), 1.74 – 1.62 (m, 2H), 1.44 (qd, J = 7.2, 14.8 Hz, 2H), 1.36 – 1.26 (m, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.99 (d, J = 6.8 Hz, 2H), 0.97 – 0.91 (m, 3H), 0.83 (t, J = 7.2 Hz, 1H), 0.37 – 0.31 (m, 2H).
103		584.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.96 – 7.86 (m, 1H), 7.76 – 7.64 (m, 1H), 7.40 – 7.30 (m, 1H), 7.29 – 7.19 (m, 1H), 7.13 (s, 1H), 6.86 – 6.78 (m, 1H), 3.67 – 3.48 (m, 1H), 3.45 – 3.35 (m, 2H), 3.29 – 3.23 (m, 2H), 3.13 – 3.03 (m, 2H), 3.03 – 2.95 (m, 2H), 2.94 – 2.85 (m, 1H), 2.77 – 2.69 (m, 2H), 2.67 (s, 3H), 2.64 – 2.55 (m, 1H), 2.54 – 2.40 (m, 2H), 2.38 – 2.28 (m, 1H), 2.26 – 2.16 (m, 4H), 2.03 – 1.84 (m, 1H), 1.74 – 1.62 (m, 2H), 1.44 (qd, J = 7.2, 14.8 Hz, 2H), 1.36 – 1.26 (m, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.99 (d, J = 6.8 Hz, 2H), 0.97 – 0.91 (m, 3H), 0.83 (t, J = 7.2 Hz, 1H), 0.37 – 0.31 (m, 2H).
104		583.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 – 7.62 (m, 1H), 7.43 – 7.27 (m, 3H), 7.03 – 6.95 (m, 1H), 6.92 – 6.79 (m, 2H), 6.70 – 6.40 (m, 3H), 5.56 (s, 1H), 4.41 – 4.24 (m, 1H), 3.80 – 3.57 (m, 4H), 3.51 – 3.38 (m, 1H), 3.15 – 2.87 (m, 5H), 2.78 – 2.54 (m, 5H), 2.04 – 1.91 (m, 1H), 1.77 – 1.62 (m, 1H), 1.11 – 0.71 (m, 7H), 0.37 – 0.24 (m, 2H).
105		583.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.63 (m, 1H), 7.42 – 7.29 (m, 3H), 7.01 – 6.96 (m, 1H), 6.90 – 6.81 (m, 2H), 6.67 – 6.62 (m, 1H), 6.59 – 6.54 (m, 1H), 6.47 – 6.41 (m, 1H), 5.59 – 5.53 (m, 1H), 4.42 – 4.34 (m, 1H), 3.80 – 3.56 (m, 4H), 3.50 – 3.40 (m, 1H), 3.31 – 3.26 (m, 1H), 3.15 – 2.98 (m, 4H), 2.97 – 2.88 (m, 1H), 2.78 – 2.68 (m, 1H), 2.60 (br s, 1H), 2.59 (br s, 2H), 2.07 (s, 1H), 1.98 (br dd, J = 6.2, 11.3 Hz, 1H), 1.76 – 1.63 (m, 1H), 1.09 – 0.72 (m, 7H), 0.35 – 0.27 (m, 2H).

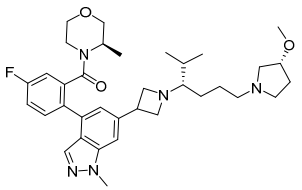
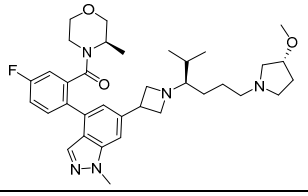
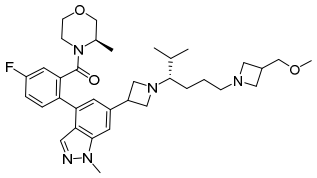
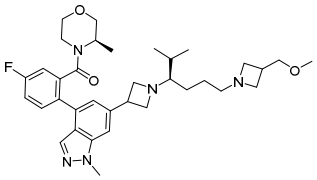
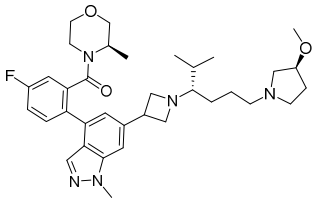
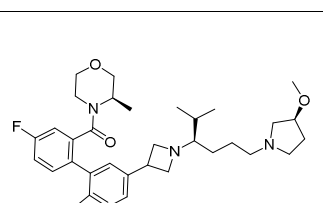
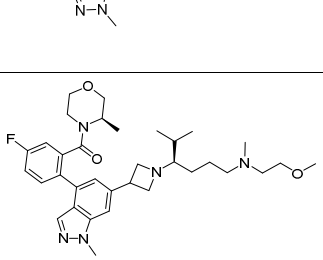
106		521.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.83 (s, 1H), 7.72 – 7.63 (m, 1H), 7.44 – 7.28 (m, 2H), 7.11 – 7.02 (m, 1H), 6.71 – 6.62 (m, 1H), 3.76 – 3.38 (m, 8H), 3.07 – 2.86 (m, 5H), 2.42 (s, 1H), 1.54 – 1.30 (m, 4H), 1.26 – 0.98 (m, 3H), 0.98 – 0.67 (m, 7H), 0.34 – 0.26 (m, 2H).
109		585.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 – 7.17 (m, 4H), 6.61 (s, 1H), 3.90 – 3.79 (m, 2H), 3.75 – 3.47 (m, 5H), 3.20 – 2.81 (m, 10H), 2.61 – 2.52 (m, 4H), 2.35 – 2.24 (m, 1H), 1.62 – 1.48 (m, 1H), 1.18 – 0.66 (m, 7H), 0.35 – 0.25 (m, 2H).
111		583.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.38 (m, 1H), 7.38 – 7.26 (m, 3H), 6.61 (s, 1H), 4.04 – 3.95 (m, 1H), 3.78 – 3.47 (m, 5H), 3.18 – 2.82 (m, 6H), 2.55 (s, 3H), 2.24 – 2.10 (m, 1H), 1.75 – 1.54 (m, 2H), 1.40 – 1.28 (m, 1H), 1.20 – 1.03 (m, 6H), 1.02 – 0.73 (m, 7H), 0.29 (br d, J = 5.9 Hz, 2H).
112		609.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 – 7.39 (m, 1H), 7.38 – 7.26 (m, 3H), 6.64 – 6.57 (m, 1H), 3.97 – 3.87 (m, 1H), 3.58 (br s, 4H), 3.08 – 2.86 (m, 6H), 2.55 (s, 3H), 2.23 – 2.09 (m, 1H), 1.96 – 1.86 (m, 1H), 1.75 – 1.57 (m, 2H), 1.51 – 1.27 (m, 6H), 1.24 – 1.00 (m, 4H), 0.99 – 0.73 (m, 7H), 0.36 – 0.24 (m, 2H).
114		555.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.39 (m, 1H), 7.38 – 7.26 (m, 3H), 6.61 (s, 1H), 3.93 – 3.86 (m, 1H), 3.73 – 3.53 (m, 5H), 3.10 (s, 1H), 3.05 – 2.81 (m, 6H), 2.69 – 2.60 (m, 1H), 2.55 (s, 3H), 2.08 – 1.96 (m, 1H), 1.73 – 1.53 (m, 3H), 1.24 – 0.74 (m, 8H), 0.34 – 0.26 (m, 2H).
116		617.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.40 (m, 1H), 7.39 – 7.28 (m, 3H), 7.14 – 7.07 (m, 3H), 7.05 – 6.99 (m, 1H), 6.63 (s, 1H), 3.99 – 3.93 (m, 1H), 3.93 – 3.87 (m, 2H), 3.85 – 3.77 (m, 1H), 3.75 – 3.52 (m, 4H), 3.22 – 2.93 (m, 5H), 2.92 – 2.80 (m, 2H), 2.76 – 2.67 (m, 1H), 2.56 (s, 3H), 1.27 – 1.11 (m, 1H), 1.07 – 0.91 (m, 3H), 0.89 – 0.82 (m, 1H), 0.82 – 0.76 (m, 3H), 0.30 (d, J = 6.4 Hz, 2H).
117		567.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.59 – 7.43 (m, 1H), 7.37 – 7.26 (m, 2H), 7.26 – 7.18 (m, 1H), 6.79 (s, 1H), 5.07 – 5.00 (m, 2H), 4.34 – 4.17 (m, 1H), 3.91 – 3.66 (m, 6H), 3.57 – 3.41 (m, 2H), 3.25 – 2.89 (m, 6H), 2.62 (s, 3H), 2.50 – 2.37 (m, 1H), 1.26 – 1.10 (m, 1H), 1.07 – 0.88 (m, 6H), 0.44 – 0.35 (m, 2H).
119		557.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 – 7.63 (m, 1H), 7.48 – 7.26 (m, 3H), 6.95 (s, 1H), 6.60 (s, 1H), 5.94 – 5.54 (m, 1H), 3.90 – 3.82 (m, 1H), 3.63 (s, 5H), 3.55 – 3.46 (m, 1H), 3.10 – 2.93 (m, 5H), 2.68 – 2.59 (m, 1H), 2.55 (s, 3H), 2.06 – 1.92 (m, 1H), 1.73 – 1.51 (m, 3H), 1.26 – 0.84 (m, 4H), 0.43 – 0.22 (m, 3H).

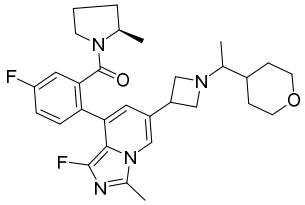
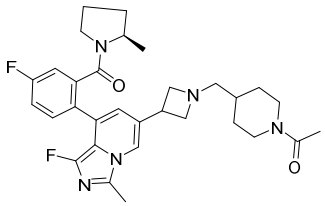
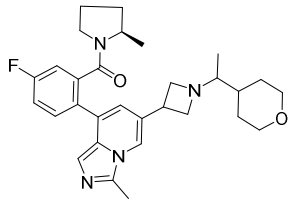
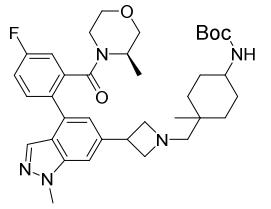
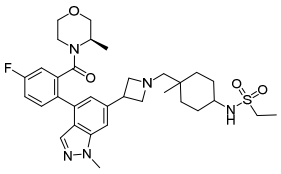
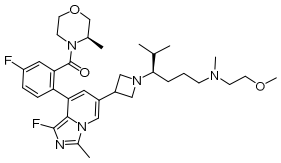
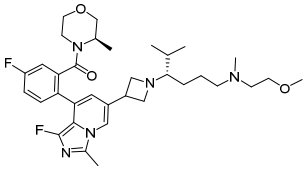
122		617.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 – 7.38 (m, 1H), 7.37 – 7.24 (m, 3H), 7.19 – 7.06 (m, 3H), 6.96 – 6.89 (m, 1H), 6.63 – 6.54 (m, 1H), 5.01 – 4.92 (m, 1H), 3.85 – 3.49 (m, 5H), 3.15 – 2.62 (m, 11H), 2.55 (s, 3H), 1.27 – 0.88 (m, 4H), 0.83 – 0.72 (m, 3H), 0.29 (s, 2H).
123		521.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.52 – 7.39 (m, 1H), 7.15 – 7.04 (m, 2H), 7.03 – 6.95 (m, 1H), 6.85 (s, 1H), 6.55 (s, 1H), 3.59 – 3.48 (m, 4H), 3.32 (t, J = 13.0 Hz, 1H), 3.26 – 3.09 (m, 2H), 3.07 (s, 2H), 2.93 – 2.89 (m, 2H), 2.88 – 2.84 (m, 2H), 2.83 – 2.75 (m, 2H), 2.73 – 2.64 (m, 1H), 2.38 (s, 3H), 1.95 – 1.81 (m, 1H), 1.77 – 1.63 (m, 1H), 0.95 – 0.63 (m, 6H), 0.57 (t, J = 7.0 Hz, 1H), 0.10 (d, J = 6.4 Hz, 2H).
124		535.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.59 – 7.43 (m, 1H), 7.37 – 7.26 (m, 2H), 7.26 – 7.18 (m, 1H), 6.79 (s, 1H), 5.07 – 5.00 (m, 2H), 4.34 – 4.17 (m, 1H), 3.91 – 3.66 (m, 6H), 3.57 – 3.41 (m, 2H), 3.25 – 2.89 (m, 6H), 2.62 (s, 3H), 2.50 – 2.37 (m, 1H), 1.26 – 1.10 (m, 1H), 1.07 – 0.88 (m, 6H), 0.44 – 0.35 (m, 2H).
125		526.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 – 10.48 (m, 1H), 7.65 – 7.43 (m, 1H), 7.40 – 7.26 (m, 1H), 7.13 – 6.69 (m, 3H), 4.78 – 4.23 (m, 4H), 4.21 – 4.03 (m, 1H), 3.94 – 3.73 (m, 1H), 3.69 – 3.54 (m, 1H), 3.33 (s, 3H), 3.08 – 2.75 (m, 1H), 2.57 (s, 3H), 2.42 – 2.13 (m, 1H), 2.09 – 1.81 (m, 3H), 1.43 – 1.10 (m, 1H), 1.08 – 0.97 (m, 1H), 0.95 – 0.86 (m, 2H), 0.83 – 0.67 (m, 3H), 0.40 – 0.22 (m, 2H).
126		540.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.62 – 7.49 (m, 1H), 7.40 – 7.16 (m, 2H), 7.03 – 6.87 (m, 1H), 4.83 – 4.63 (m, 2H), 4.55 – 4.32 (m, 2H), 4.18 – 3.94 (m, 3H), 3.88 – 3.69 (m, 1H), 3.55 – 3.37 (m, 2H), 3.22 – 2.94 (m, 2H), 2.67 (s, 3H), 2.28 – 2.09 (m, 1H), 2.03 – 1.84 (m, 2H), 1.82 – 1.61 (m, 3H), 1.45 – 1.28 (m, 1H), 1.20 – 1.12 (m, 1H), 1.08 – 1.02 (m, 2H), 0.97 – 0.87 (m, 3H), 0.48 – 0.38 (m, 2H).
127		631.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.02 (m, 9H), 6.57 – 6.37 (m, 1H), 4.29 – 3.90 (m, 1H), 3.70 – 3.43 (m, 3H), 3.38 – 3.19 (m, 5H), 3.14 – 2.58 (m, 7H), 2.53 (s, 3H), 2.35 – 2.06 (m, 1H), 1.89 – 1.68 (m, 1H), 1.25 – 0.67 (m, 7H), 0.38 – 0.17 (m, 2H).
129		568.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.01 (m, 1H), 7.69 (s, 1H), 7.49 – 7.28 (m, 2H), 7.07 – 6.97 (m, 1H), 6.71 – 6.54 (m, 1H), 5.96 – 5.46 (m, 1H), 4.72 – 4.04 (m, 4H), 4.02 – 3.81 (m, 2H), 3.69 – 3.47 (m, 3H), 2.80 – 2.67 (m, 1H), 2.59 (s, 3H), 2.04 – 1.22 (m, 10H), 1.00 – 0.81 (m, 3H), 0.33 (s, 3H).

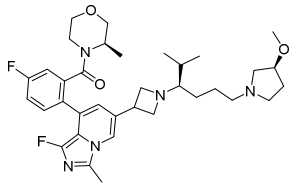
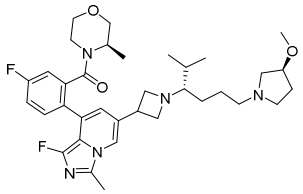
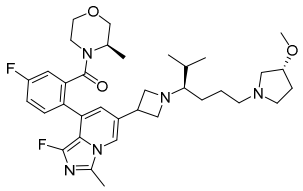
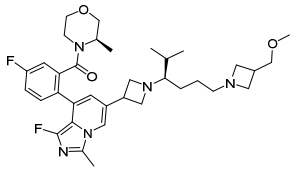
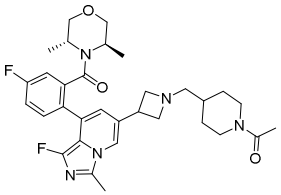
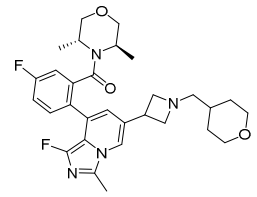
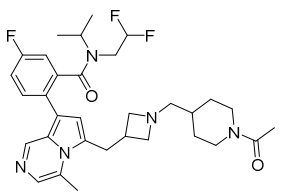
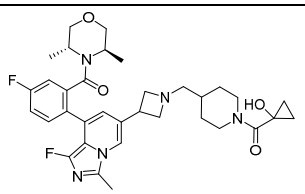
130		522.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.60 – 7.48 (m, 1H), 7.42 – 7.28 (m, 2H), 6.65 – 6.51 (m, 1H), 5.00 – 4.80 (m, 2H), 4.68 – 4.43 (m, 1H), 4.33 – 4.11 (m, 2H), 4.01 – 3.77 (m, 2H), 3.75 – 3.63 (m, 1H), 3.59 – 3.41 (m, 2H), 3.09 – 2.75 (m, 2H), 2.72 – 2.53 (m, 5H), 2.44 – 2.28 (m, 1H), 1.17 – 0.73 (m, 7H), 0.53 – 0.33 (m, 2H).
133		542.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.80 – 7.61 (m, 1H), 7.38 (t, J = 8.2 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 6.89 – 6.79 (m, 1H), 6.06 – 5.52 (m, 1H), 4.78 – 4.56 (m, 1H), 4.48 – 4.23 (m, 2H), 4.16 – 3.88 (m, 2H), 3.81 – 3.58 (m, 2H), 3.46 – 3.31 (m, 2H), 3.15 – 3.00 (m, 1H), 2.67 (s, 4H), 1.97 – 1.74 (m, 2H), 1.65 – 1.38 (m, 4H), 1.02 – 0.90 (m, 3H), 0.60 – 0.17 (m, 3H).
135		612.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.51 (m, 2H), 7.26 – 7.13 (m, 3H), 7.00 (br s, 1H), 4.63 – 4.10 (m, 1H), 4.06 – 3.95 (m, 1H), 3.82 – 3.36 (m, 5H), 3.31 – 3.11 (m, 4H), 3.04 (q, J = 7.2 Hz, 2H), 2.99 – 2.84 (m, 1H), 2.69 (s, 3H), 2.45 – 2.33 (m, 2H), 2.13 – 2.03 (m, 2H), 1.94 – 1.72 (m, 4H), 1.37 (t, J = 7.6 Hz, 3H), 1.33 – 1.16 (m, 4H), 1.14 – 0.97 (m, 3H), 0.80 – 0.42 (m, 1H).
137		616.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.56 – 7.47 (m, 1H), 7.39 – 7.25 (m, 2H), 7.00 – 6.94 (m, 1H), 6.72 – 6.60 (m, 1H), 3.46 (s, 4H), 3.13 – 2.90 (m, 6H), 2.53 (s, 3H), 2.28 – 2.18 (m, 2H), 2.08 – 1.63 (m, 5H), 1.21 – 1.11 (m, 6H), 0.97 – 0.75 (m, 9H), 0.39 (s, 2H).
138		634.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.72 – 7.64 (m, 1H), 7.48 – 7.23 (m, 2H), 7.04 – 6.91 (m, 2H), 6.75 (s, 1H), 5.91 – 5.58 (m, 1H), 3.68 – 3.46 (m, 5H), 3.01 (s, 5H), 2.62 – 2.54 (m, 3H), 2.34 – 2.19 (m, 2H), 1.89 – 1.67 (m, 4H), 1.26 – 1.11 (m, 6H), 1.01 – 0.84 (m, 5H), 0.37 – 0.23 (m, 3H).
144		568.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 11.6 Hz, 1H), 7.53 – 7.42 (m, 1H), 7.17 (dt, J = 8.4, 8.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.93 – 6.88 (m, 1H), 6.53 – 6.47 (m, 1H), 5.81 – 5.34 (m, 1H), 4.87 – 4.74 (m, 2H), 4.54 – 4.43 (m, 1H), 4.02 – 3.88 (m, 2H), 3.59 – 3.36 (m, 3H), 3.29 – 3.18 (m, 1H), 3.07 – 2.99 (m, 1H), 2.76 – 2.56 (m, 3H), 2.49 – 2.42 (m, 3H), 2.33 – 2.13 (m, 1H), 1.85 – 1.71 (m, 2H), 1.61 – 1.36 (m, 2H), 1.27 – 1.06 (m, 1H), 1.01 – 0.51 (m, 4H), 0.33 – 0.01 (m, 3H).
148		558.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.75 – 7.68 (m, 1H), 7.43 – 7.34 (m, 1H), 7.33 – 7.28 (m, 1H), 7.16 – 7.11 (m, 1H), 6.92 – 6.77 (m, 1H), 5.99 – 5.64 (m, 1H), 3.83 – 3.77 (m, 1H), 3.77 – 3.69 (m, 2H), 3.69 – 3.62 (m, 2H), 3.29 – 3.24 (m, 2H), 2.75 – 2.68 (m, 2H), 2.66 (s, 3H), 2.50 (s, 3H), 2.27 – 2.23 (m, 1H), 2.20 – 2.03 (m, 1H), 1.92 – 1.84 (m, 1H), 1.67 – 1.59 (m, 2H), 1.46 – 1.37 (m, 2H), 1.36 – 1.32 (m, 2H), 1.29 (s, 3H), 0.98 – 0.95 (m, 3H), 0.94 – 0.89 (m, 3H), 0.36 – 0.32 (m, 2H).

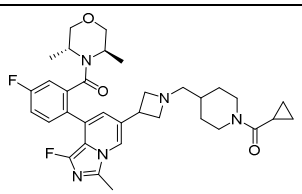
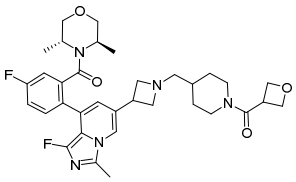
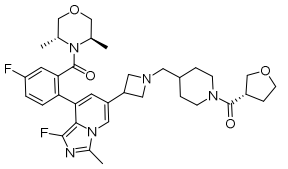
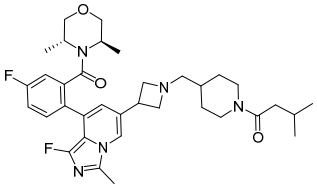
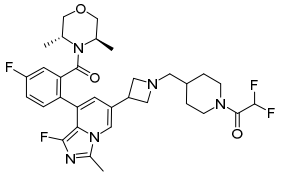
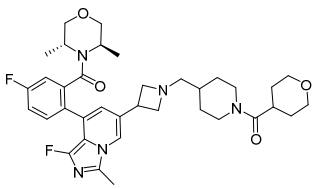
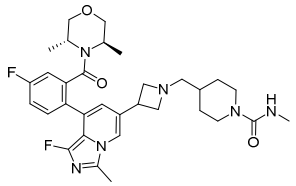
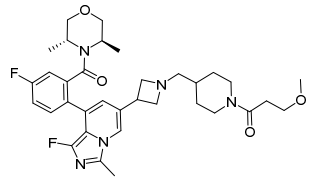
149		616.6	^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.75 – 7.68 (m, 1H), 7.42 – 7.35 (m, 1H), 7.30 (dd, J = 2.8, 8.8 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.91 – 6.82 (m, J = 2.6 Hz, 1H), 6.01 – 5.63 (m, 1H), 3.85 – 3.79 (m, 1H), 3.79 – 3.61 (m, 4H), 3.57 – 3.51 (m, 2H), 3.34 (d, J = 3.2 Hz, 3H), 2.78 – 2.71 (m, 2H), 2.66 (s, 3H), 2.60 – 2.53 (m, 2H), 2.39 (d, J = 2.8 Hz, 3H), 2.31 – 2.26 (m, 1H), 1.94 – 1.83 (m, 1H), 1.67 – 1.58 (m, 2H), 1.45 – 1.27 (m, 6H), 0.98 – 0.91 (m, 9H), 0.35 (br d, J = 6.5 Hz, 2H).
151		654.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.64 – 7.49 (m, 1H), 7.40 – 7.22 (m, 2H), 6.73 – 6.56 (m, 1H), 6.14 – 5.72 (m, 1H), 4.08 – 3.93 (m, 1H), 3.84 – 3.59 (m, 5H), 3.40 – 3.32 (m, 2H), 3.30 – 3.20 (m, 3H), 3.17 – 2.97 (m, 3H), 2.67 – 2.53 (m, 5H), 2.17 – 2.03 (m, 1H), 1.77 – 1.63 (m, 1H), 1.56 – 1.39 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.06 – 0.94 (m, 3H), 0.45 (s, 3H).
155		574.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.64 – 7.50 (m, 1H), 7.47 – 7.26 (m, 2H), 6.59 – 6.41 (m, 1H), 6.15 – 5.70 (m, 1H), 4.72 – 4.40 (m, 1H), 4.33 – 4.04 (m, 2H), 3.98 – 3.39 (m, 6H), 2.85 – 2.63 (m, 2H), 2.55 (s, 3H), 1.92 – 1.62 (m, 2H), 1.57 – 1.41 (m, 1H), 1.30 – 1.14 (m, 1H), 1.06 – 0.86 (m, 7H), 0.43 (s, 3H).
156		560.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.64 – 7.24 (m, 3H), 6.64 – 6.35 (m, 1H), 6.17 – 5.65 (m, 1H), 4.70 – 4.44 (m, 1H), 4.40 – 3.77 (m, 5H), 3.73 – 3.46 (m, 3H), 3.12 (s, 1H), 3.00 – 2.70 (m, 2H), 2.55 (s, 3H), 2.13 (s, 1H), 1.82 (s, 1H), 1.51 – 1.19 (m, 1H), 1.09 – 0.89 (m, 6H), 0.43 (s, 3H).
158		658.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 7.53 – 7.47 (m, 1H), 7.40 (s, 1H), 7.28 – 7.19 (m, 1H), 7.14 (dd, J = 2.8, 8.8 Hz, 1H), 6.97 (s, 1H), 5.78 – 5.39 (m, 1H), 3.95 (s, 3H), 3.88 – 3.79 (m, 1H), 3.50 – 3.39 (m, 3H), 3.38 – 3.29 (m, 2H), 3.15 – 3.10 (m, 1H), 2.97 – 2.86 (m, 2H), 2.77 – 2.66 (m, 1H), 2.61 – 2.48 (m, 3H), 2.29 – 2.19 (m, 1H), 1.92 – 1.83 (m, 3H), 1.65 – 1.57 (m, 1H), 1.29 (s, 12H), 0.77 (d, J = 6.4 Hz, 3H), 0.01 (d, J = 6.4 Hz, 3H).
160		626.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.73 (m, 1H), 7.72 – 7.51 (m, 2H), 7.50 – 7.27 (m, 2H), 7.21 – 6.92 (m, 2H), 4.34 – 3.38 (m, 9H), 3.23 – 2.66 (m, 8H), 2.43 (d, J = 6.8 Hz, 2H), 1.90 – 1.66 (m, 4H), 1.43 – 0.87 (m, 13H), 0.52 – 0.15 (m, 1H).
162		594.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.90 – 7.76 (m, 1H), 7.66 – 7.45 (m, 1H), 7.29 – 7.05 (m, 4H), 4.54 – 4.20 (m, 1H), 4.16 – 3.93 (m, 6H), 3.63 – 2.90 (m, 11H), 2.85 – 2.47 (m, 6H), 2.41 – 2.32 (m, 4H), 1.95 – 1.77 (m, 1H), 1.69 – 1.54 (m, 2H), 1.46 – 1.34 (m, 2H), 1.24 – 1.16 (m, 1H), 1.04 – 0.87 (m, 7H), 0.53 – 0.08 (m, 1H).

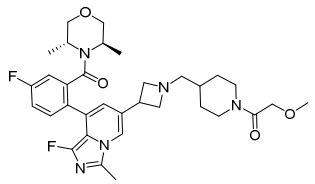
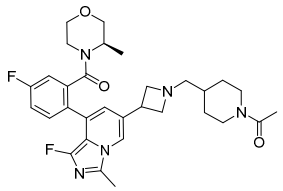
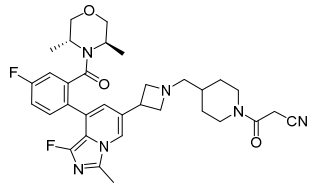
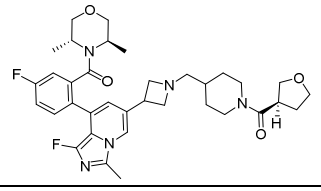
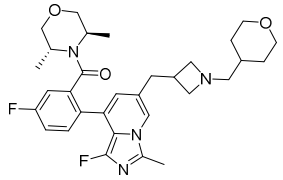
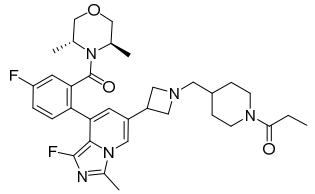
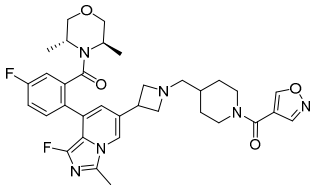
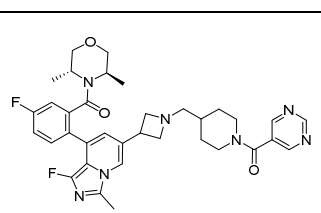
167		596.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.74 (m, 1H), 7.70 – 7.58 (m, 1H), 7.55 – 7.49 (m, 1H), 7.45 – 7.25 (m, 2H), 7.14 – 6.92 (m, 2H), 4.12 – 4.03 (m, 3H), 3.94 – 3.82 (m, 1H), 3.77 – 3.67 (m, 1H), 3.67 – 3.59 (m, J = 6.0 Hz, 2H), 3.18 – 3.04 (m, 2H), 3.02 – 2.64 (m, 5H), 2.35 – 2.18 (m, 2H), 1.93 – 1.64 (m, 5H), 1.59 – 1.23 (m, 3H), 1.22 – 1.12 (m, 6H), 0.99 – 0.64 (m, 5H).
168		626.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 – 7.33 (m, 5H), 7.07 – 6.86 (m, 2H), 4.06 (s, 3H), 3.80 – 3.48 (m, 5H), 3.19 – 2.91 (m, 7H), 2.42 – 2.07 (m, 4H), 1.90 – 1.71 (m, 4H), 1.22 – 1.12 (m, 6H), 1.04 – 0.80 (m, 5H), 0.62 (s, 3H).
172		563.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.73 – 7.52 (m, 2H), 7.51 – 7.20 (m, 2H), 7.19 – 6.87 (m, 1H), 6.55 – 6.26 (m, 1H), 4.34 – 3.37 (m, 11H), 3.25 – 2.69 (m, 5H), 2.69 – 2.52 (m, 5H), 2.38 – 2.21 (m, 2H), 1.85 – 1.21 (m, 4H), 1.21 – 0.85 (m, 4H), 0.56 – 0.13 (m, 1H).
173		573.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.70 – 7.55 (m, 2H), 7.49 – 7.25 (m, 2H), 7.20 – 6.93 (m, 1H), 4.34 – 3.45 (m, 13H), 3.17 – 2.54 (m, 7H), 2.45 – 2.17 (m, 3H), 1.81 – 1.44 (m, 3H), 1.19 – 0.86 (m, 4H), 0.52 – 0.06 (m, 1H).
176		626.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.71 – 7.54 (m, 1H), 7.49 – 7.25 (m, 2H), 7.17 – 6.69 (m, 2H), 4.32 – 3.91 (m, 5H), 3.82 – 3.02 (m, 12H), 2.93 – 2.85 (m, 2H), 2.80 – 2.67 (m, 2H), 2.32 – 2.26 (m, 1H), 2.19 – 2.03 (m, 1H), 1.88 – 1.68 (m, 2H), 1.39 – 1.17 (m, 2H), 1.14 – 0.77 (m, 10H), 0.50 – 0.11 (m, 1H).
177		548.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.53 – 7.38 (m, 2H), 7.31 – 7.10 (m, 2H), 7.02 – 6.77 (m, 1H), 4.18 – 3.86 (m, 5H), 3.71 – 3.46 (m, 5H), 3.44 – 3.18 (m, 2H), 3.02 – 2.50 (m, 6H), 2.19 – 2.14 (m, 2H), 1.83 – 1.77 (m, 3H), 1.63 – 1.49 (m, 2H), 1.42 – 1.06 (m, 2H), 1.00 – 0.86 (m, 2H), 0.83 – 0.73 (m, 2H), 0.33 – 0.00 (m, 1H).
179		608.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.73 – 7.62 (m, 1H), 7.49 – 7.35 (m, 1H), 7.28 – 7.01 (m, 3H), 6.88 – 6.74 (m, 1H), 4.26 – 3.95 (m, 1H), 3.92 – 3.76 (m, 3H), 3.46 – 3.20 (m, 6H), 3.13 (s, 4H), 3.07 – 2.91 (m, 1H), 2.85 – 2.77 (m, 4H), 2.75 – 2.54 (m, 2H), 2.34 (s, 2H), 2.25 – 2.15 (m, 2H), 2.10 – 2.04 (m, 3H), 1.95 (s, 1H), 1.72 – 1.59 (m, 1H), 1.43 – 1.12 (m, 4H), 1.09 – 1.00 (m, 2H), 0.91 – 0.81 (m, 1H), 0.77 – 0.73 (m, 3H), 0.71 – 0.67 (m, 3H), 0.30 - -0.03 (m, 1H).
180		616.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.71 – 7.59 (m, 1H), 7.50 (s, 1H), 7.44 – 7.34 (m, 1H), 7.32 – 7.23 (m, 1H), 7.18 – 7.06 (m, 1H), 5.91 – 5.58 (m, 2H), 4.08 (s, 3H), 3.94 – 3.78 (m, 4H), 3.60 – 3.47 (m, 4H), 2.68 – 2.60 (m, 2H), 2.48 – 2.41 (m, 2H), 2.30 (s, 3H), 2.28 – 2.21 (m, 1H), 1.97 – 1.81 (m, 2H), 1.67 – 1.54 (m, 3H), 1.44 – 1.25 (m,

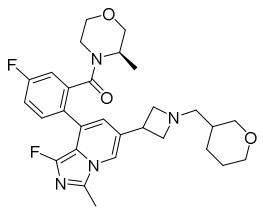
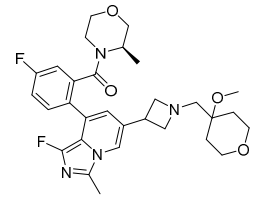
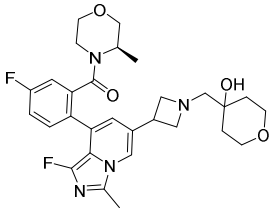
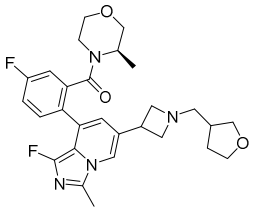
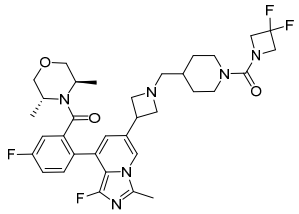
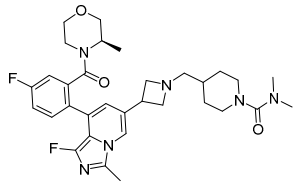
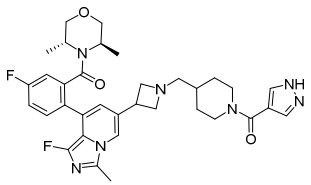
			6H), 0.97 – 0.88 (m, 8H), 0.14 – 0.10 (m, 2H).
182-1		606.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.81 (m, 1H), 7.71 – 7.52 (m, 1H), 7.41 – 7.27 (m, 2H), 7.26 – 7.08 (m, 2H), 4.63 – 4.27 (m, 1H), 4.14 (s, 3H), 4.07 – 3.97 (m, 3H), 3.70 – 3.51 (m, 2H), 3.51 – 3.37 (m, 3H), 3.33 – 3.27 (m, 3H), 3.24 – 3.12 (m, 1H), 3.04 – 2.93 (m, 2H), 2.90 – 2.81 (m, 2H), 2.80 – 2.70 (m, 2H), 2.61 – 2.34 (m, 2H), 2.27 – 2.07 (m, 1H), 2.04 – 1.84 (m, 2H), 1.78 – 1.67 (m, 2H), 1.54 – 1.37 (m, 2H), 1.32 – 1.21 (m, 2H), 1.10 – 1.03 (m, 1H), 1.02 – 0.87 (m, 6H), 0.59 – 0.06 (m, 2H).
182-2		606.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.98 – 7.80 (m, 1H), 7.77 – 7.57 (m, 1H), 7.57 – 7.45 (m, 1H), 7.42 – 7.06 (m, 3H), 4.52 – 4.02 (m, 4H), 4.01 – 3.34 (m, 7H), 3.28 – 2.64 (m, 9H), 2.59 – 2.23 (m, 5H), 2.16 – 2.02 (m, 1H), 1.96 – 1.76 (m, 2H), 1.70 – 1.19 (m, 6H), 1.11 – 0.86 (m, 7H), 0.56 – 0.14 (m, 1H).
183-1		606.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.91 – 7.84 (m, 1H), 7.72 – 7.50 (m, 2H), 7.42 – 7.34 (m, 1H), 7.34 – 7.20 (m, 2H), 4.12 – 4.08 (m, 3H), 3.99 – 3.78 (m, 4H), 3.49 – 3.45 (m, 2H), 3.41 (t, J = 7.8 Hz, 2H), 3.34 – 3.32 (m, 3H), 3.29 – 3.17 (m, 2H), 3.08 – 2.97 (m, 3H), 2.97 – 2.80 (m, 1H), 2.72 (td, J = 6.8, 13.2 Hz, 1H), 2.56 – 2.32 (m, 3H), 2.27 – 2.01 (m, 2H), 1.93 – 1.82 (m, 1H), 1.51 – 1.37 (m, 4H), 1.36 – 1.26 (m, 2H), 1.23 (d, J = 6.8 Hz, 1H), 1.06 (d, J = 6.8 Hz, 1H), 0.97 – 0.90 (m, 6H), 0.51 (d, J = 6.8 Hz, 1H).
183-2		606.4	^{1}H NMR (400 MHz, CD3OD) δ 7.96 – 7.79 (m, 1H), 7.77 – 7.45 (m, 2H), 7.43 – 7.07 (m, 3H), 4.49 – 4.03 (m, 4H), 4.00 – 3.80 (m, 3H), 3.66 – 3.33 (m, 9H), 3.28 – 2.69 (m, 7H), 2.60 – 2.19 (m, 4H), 1.95 – 1.81 (m, 1H), 1.56 – 1.18 (m, 6H), 1.10 – 0.87 (m, 7H), 0.55 – 0.14 (m, 1H).
184-1		606.4	^{1}H NMR (400 MHz, CD3OD) δ 7.92 – 7.86 (m, 1H), 7.74 – 7.67 (m, 1H), 7.64 – 7.54 (m, 1H), 7.43 – 7.36 (m, 1H), 7.35 – 7.22 (m, 2H), 4.13 – 4.10 (m, 3H), 4.07 – 4.00 (m, 2H), 4.00 – 3.91 (m, 3H), 3.53 – 3.43 (m, 3H), 3.13 – 2.97 (m, 4H), 2.91 – 2.77 (m, 4H), 2.55 – 2.35 (m, 2H), 2.20 – 2.11 (m, 1H), 2.05 – 1.95 (m, 2H), 1.91 (s, 3H), 1.78 – 1.69 (m, 2H), 1.40 – 1.33 (m, 2H), 1.31 – 1.28 (m, 2H), 1.24 (d, J = 6.8 Hz, 1H), 1.07 (d, J = 6.8 Hz, 1H), 1.00 (t, J = 6.2 Hz, 3H), 0.97 – 0.93 (m, 3H), 0.50 (d, J = 6.8 Hz, 1H).
184-2		606.4	^{1}H NMR (400 MHz, CD3OD) δ 7.95 – 7.83 (m, 1H), 7.72 – 7.57 (m, 1H), 7.56 – 7.45 (m, 1H), 7.42 – 7.31 (m, 1H), 7.31 – 7.07 (m, 2H), 4.47 – 4.26 (m, 1H), 4.13 – 4.07 (m, 3H), 4.00 – 3.80 (m, 5H), 3.65 – 3.40 (m, 2H), 3.27 – 3.23 (m, 3H), 3.13 (s, 2H), 2.74 – 2.73 (m, 1H), 2.78 – 2.61 (m, 3H), 2.56 – 2.37 (m, 4H), 2.25 (s, 1H), 2.13 – 2.00 (m, 1H), 1.93 – 1.84 (m, 1H), 1.83 – 1.74 (m, 1H), 1.67 – 1.55 (m, 2H), 1.52 – 1.27 (m, 3H), 1.25 – 1.21 (m, 1H), 1.08 – 1.04 (m, 1H), 0.99 – 0.90 (m, 6H), 0.54 – 0.13 (m, 1H).
185		594.4	^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 – 7.75 (m, 1H), 7.70 – 7.53 (m, 2H), 7.50 – 7.21 (m, 2H), 7.15 – 6.91 (m, 1H), 4.33 – 4.11 (m, 1H), 4.09 – 4.03 (m, 3H), 3.87 – 3.54 (m, 4H), 3.52 – 3.36 (m, 4H), 3.20 (s, 3H), 3.18 – 3.01 (m, 4H), 2.94 – 2.72 (m, 1H), 2.47 – 2.42 (m, 2H), 2.31 – 2.23 (m, 2H), 2.14 (s, 3H), 2.08 – 1.99 (m, 1H), 1.78 – 1.68 (m,

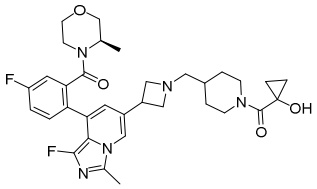
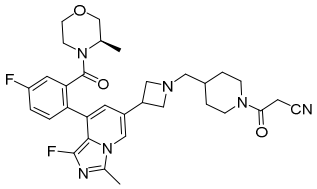
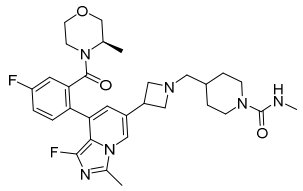
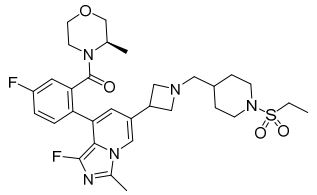
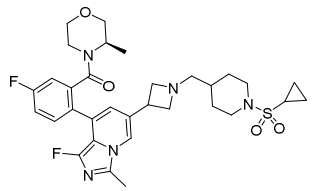
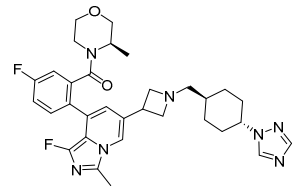
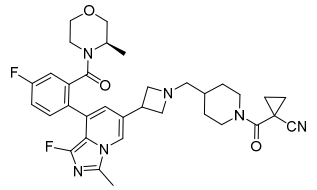
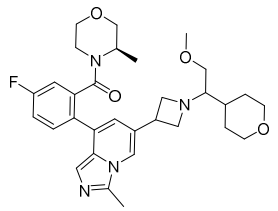
			1H), 1.48 – 1.37 (m, 2H), 1.30 – 1.18 (m, 2H), 1.12 (d, J = 6.8 Hz, 1H), 0.98 (d, J = 6.8 Hz, 1H), 0.89 – 0.82 (m, 6H), 0.51 – 0.14 (m, 1H).
188		523.3	^{1}H NMR (400 MHz, DMSO-d6) δ 7.82 (s, 1H), 7.59 – 7.48 (m, 1H), 7.42 – 7.28 (m, 2H), 6.75 – 6.53 (m, 1H), 4.00 – 3.79 (m, 3H), 3.56 – 3.42 (m, 3H), 3.30 – 3.17 (m, 3H), 3.12 – 3.00 (m, 3H), 2.54 (s, 3H), 2.19 – 2.11 (m, 1H), 1.93 – 1.73 (m, 1H), 1.64 – 1.45 (m, 4H), 1.40 – 1.18 (m, 4H), 0.96 – 0.74 (m, 6H).
189		550.3	^{1}H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 0.79H), 7.83 (s, 1H), 7.59 – 7.50 (m, 1H), 7.42 – 7.29 (m, 2H), 6.76 – 6.59 (m, 1H), 4.37 – 4.28 (m, 1H), 3.98 – 3.89 (m, 1H), 3.82 – 3.70 (m, 2H), 3.27 – 2.89 (m, 7H), 2.54 (s, 3H), 2.48 – 2.42 (m, 1H), 2.37 – 2.32 (m, 2H), 1.96 (s, 3H), 1.91 – 1.78 (m, 1H), 1.74 – 1.31 (m, 6H), 1.10 – 0.75 (m, 5H).
190		505.4	^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (s, 1H), 7.79 – 7.65 (m, 1H), 7.44 – 7.30 (m, 2H), 7.11 – 7.00 (m, 1H), 6.87 – 6.69 (m, 1H), 3.96 – 3.81 (m, 3H), 3.58 – 3.45 (m, 3H), 3.29 – 3.17 (m, 3H), 3.13 – 2.97 (m, 3H), 2.59 (s, 3H), 2.16 (s, 1H), 1.89 – 1.73 (m, 1H), 1.63 – 1.44 (m, 4H), 1.38 – 1.26 (m, 3H), 1.25 – 1.16 (m, 1H), 0.88 (s, 2H), 0.81 – 0.72 (m, 4H).
192		634.3	^{1}H NMR (400 MHz, CD3OD) δ 8.55 – 8.48 (m, 1H), 7.99 – 7.86 (m, 1H), 7.75 – 7.55 (m, 2H), 7.52 – 7.11 (m, 4H), 4.63 – 4.17 (m, 4H), 4.14 – 3.99 (m, 5H), 3.85 – 3.38 (m, 5H), 3.23 – 3.00 (m, 2H), 2.96 – 2.81 (m, 3H), 2.56 – 2.26 (m, 1H), 1.77 – 1.60 (m, 5H), 1.44 (s, 9H), 1.24 (d, J = 6.8 Hz, 2H), 1.00 (s, 3H), 0.51 – 0.16 (m, 1H).
193		626.2	^{1}H NMR (400 MHz, CD3OD) δ 8.02 – 7.81 (m, 1H), 7.80 – 7.51 (m, 2H), 7.49 – 7.07 (m, 3H), 4.67 – 4.24 (m, 3H), 4.18 – 3.89 (m, 3H), 3.61 – 3.38 (m, 3H), 3.25 – 3.02 (m, 3H), 3.00 – 2.87 (m, 1H), 2.86 – 2.77 (m, 3H), 2.52 – 2.18 (m, 1H), 1.95 – 1.68 (m, 4H), 1.66 – 1.51 (m, 2H), 1.49 – 1.36 (m, 2H), 1.35 – 1.26 (m, 7H), 1.25 – 1.20 (m, 1H), 1.13 – 1.07 (m, 3H), 0.48 – 0.19 (m, 1H).
200-1		612.3	^{1}H NMR (400 MHz, DMSO-d6) δ 8.00 – 7.68 (m, 1H), 7.64 – 7.20 (m, 3H), 6.70 (s, 1H), 4.40 – 3.34 (m, 9H), 3.20 (s, 3H), 3.17 – 2.51 (m, 8H), 2.47 – 2.38 (m, 2H), 2.31 – 2.23 (m, 2H), 2.13 (s, 3H), 2.06 – 1.98 (m, 1H), 1.78 – 1.62 (m, 1H), 1.51 – 1.01 (m, 6H), 0.90 – 0.65 (m, 7H).
200-2		612.4	^{1}H NMR (400 MHz, CDCl3) δ 7.61 – 7.35 (m, 2H), 7.25 – 7.03 (m, 2H), 6.84 – 6.55 (m, 1H), 5.40 – 4.10 (m, 1H), 3.76 – 3.65 (m, 2H), 3.62 – 3.46 (m, 4H), 3.35 (s, 3H), 3.22 – 3.11 (m, 2H), 3.07 – 2.71 (m, 2H), 2.61 (s, 3H), 2.47 – 2.36 (m, 2H), 2.30 (br s, 3H), 2.17 – 2.00 (m, 2H), 1.88 – 1.76 (m, 3H), 1.61 – 1.52 (m, 2H), 1.35 – 1.24 (m, 4H), 1.19 – 1.08 (m, 1H), 0.95 – 0.87 (m, 6H), 0.86 – 0.80 (m, 1H), 0.79 – 0.06 (m, 1H).

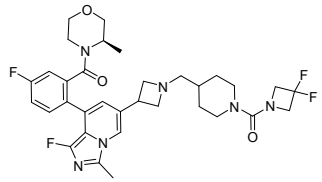
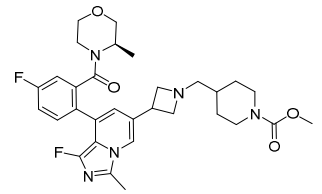
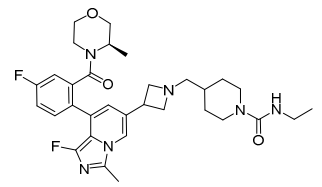
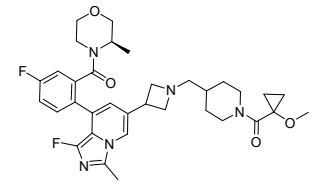
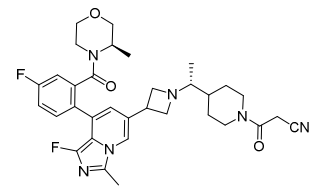
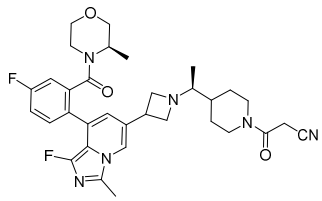
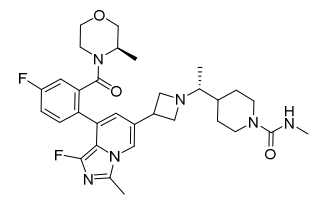
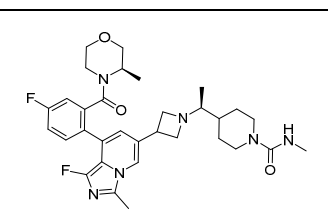
201-1		624.3	^{1}H NMR (400 MHz, CD3OD) δ 7.89 – 7.71 (m, 1H), 7.67 – 7.49 (m, 1H), 7.40 – 7.14 (m, 2H), 6.86 – 6.59 (m, 1H), 4.62 – 4.32 (m, 1H), 4.10 – 3.90 (m, 1H), 3.81 – 3.52 (m, 5H), 3.29 – 3.21 (m, 5H), 3.18 – 2.83 (m, 2H), 2.78 – 2.64 (m, 3H), 2.63 – 2.56 (m, 3H), 2.56 – 2.40 (m, 3H), 2.38 – 1.97 (m, 3H), 1.92 – 1.73 (m, 2H), 1.70 – 1.52 (m, 2H), 1.48 – 1.13 (m, 4H), 1.09 – 0.51 (m, 8H).
201-2		624.4	^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 7.37 (m, 2H), 7.24 – 7.05 (m, 2H), 6.78 – 6.55 (m, 1H), 5.38 – 4.10 (m,1H), 3.97 – 3.88 (m, 1H), 3.76 – 3.65 (m, 2H), 3.62 – 3.33 (m, 3H), 3.28 (s, 3H), 3.19 – 3.09 (m, 2H), 3.06 – 2.91 (m, 1H),2.83 – 2.75 (m, 1H), 2.73 – 2.65 (m, 1H), 2.61 (s, 3H), 2.59 – 2.52 (m, 1H), 2.49 – 2.39 (m, 2H), 2.14 – 2.03 (m, 3H), 1.99 -1.91 (m, 1H), 1.88 – 1.72 (m, 3H), 1.67 – 1.54 (m, 2H), 1.35 – 1.25 (m, 3H), 1.19 – 1.07 (m, 1H), 0.89 (br t, J = 7.6 Hz, 6H),0.85 – 0.69 (m, 1H), 0.68 – 0.04 (m, 1H).
202		624.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 2H), 7.12 (br s, 2H), 6.73 – 6.45 (m, 1H), 4.58 – 4.03 (m, 1H), 3.89-3.24 (m, 7H), 3.20 (s, 3H), 3.17 – 2.84 (m, 4H), 2.74 – 2.52 (m, 5H), 2.52 – 2.29 (m, 4H), 2.03 – 1.91 (m, 2H), 1.78 – 1.68 (m,2H), 1.54 – 1.41 (m, 2H), 1.34 – 1.01 (m, 4H), 0.99 – 0.49 (m, 8H).
203		624.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.51 (m, 2H), 7.36 – 7.13 (m, 2H), 6.87 – 6.59 (m, 1H), 4.74 – 3.98 (m, 2H),3.86 – 3.53 (m, 5H), 3.52 – 3.36 (m, 5H), 3.33 (s, 3H), 3.25 – 2.95 (m, 5H), 2.77 – 2.69 (m, 1H), 2.60 (s, 3H), 2.52 – 2.40 (m,2H), 2.27 – 2.13 (m, 1H), 1.91 – 1.15 (m, 8H), 0.97 – 0.86 (m, 6H), 0.83 – 0.59 (m, 1H).
205		580.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.55 – 7.47 (m, 1H), 7.46 – 7.34 (m, 2H), 6.61 (s, 1H), 4.32 (s, 1H), 3.80 – 3.47 (m, 6H), 3.28 – 2.88 (m, 5H), 2.80 – 2.52 (m, 4H), 2.49 – 2.41 (m, 2H), 2.30 (d, J = 6.8 Hz, 2H), 1.96 (s, 3H), 1.76 – 1.59 (m, 2H), 1.55 – 1.41 (m, 1H), 1.15 – 0.58 (m, 8H).
208		539.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.58 – 7.46 (m, 1H), 7.38 – 7.27 (m, 2H), 6.67 (s, 1H), 3.96 – 3.88 (m, 4H), 3.86 – 3.75 (m, 2H), 3.55 – 3.46 (m, 2H), 3.41 (dt, J = 1.6, 12.0 Hz, 3H), 2.69 – 2.62 (m, 2H), 2.61 (s, 3H), 1.80 – 1.70 (m, 1H), 1.70 – 1.62 (m, 2H), 1.42 – 1.23 (m, 6H), 1.19 – 1.01 (m, 4H), 0.93 – 0.82 (m, 2H).
210		584.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 7.59 – 7.50 (m, 1H), 7.33 (dt, J = 2.4, 8.4 Hz, 1H), 7.26 – 7.11 (m, 2H), 6.68 (s, 1H), 6.14 – 5.71 (m, 1H), 4.55 – 4.43 (m, 1H), 3.95 – 3.84 (m, 1H), 3.71 – 3.50 (m, 6H), 3.41 – 3.32 (m, 1H), 3.12 – 2.99 (m, 3H), 2.93 (td, J = 6.8, 14.0 Hz, 1H), 2.83 (s, 3H), 2.64 – 2.54 (m, 1H), 2.43 (d, J = 6.8 Hz, 2H), 2.07 (s, 3H), 1.83 – 1.59 (m, 3H), 1.33 – 0.99 (m, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.34 (d, J = 6.8 Hz, 2H).
214		622.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 7.24 – 7.16 (m, 2H), 6.66 (s, 1H), 4.52 (s, 2H), 3.98 – 3.57(m, 6H), 3.43 – 3.04 (m, 6H), 2.94 – 2.64 (m, 4H), 2.62 (s, 3H), 2.54 – 2.40 (m, 2H), 1.85 – 1.75 (m, 3H), 1.30 – 1.18 (m,3H), 1.14 – 1.08 (m, 4H), 1.05 – 1.02 (m, 1H), 0.98 – 0.94 (m, 2H).

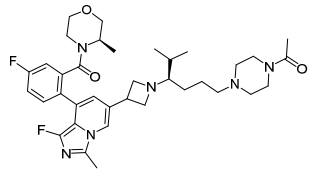
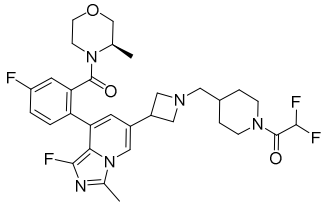
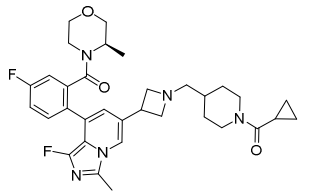
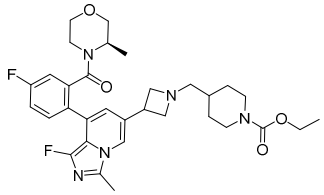
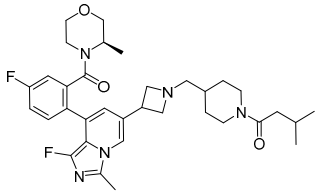
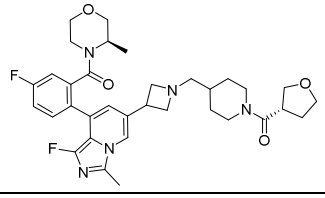
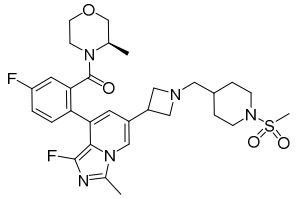
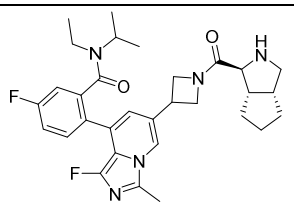
215		606.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.25 – 7.15 (m, 2H), 6.61 (s, 1H), 4.64 – 4.50 (m, 1H), 4.21(d, J = 12.8 Hz, 1H), 3.92 – 3.56 (m, 5H), 3.46 – 2.74 (m, 7H), 2.62 (s, 3H), 2.60 – 2.53 (m, 1H), 2.46 – 2.36 (m, 2H), 1.91 -1.80 (m, 1H), 1.78 – 1.71 (m, 2H), 1.28 – 0.87 (m, 11H), 0.79 – 0.69 (m, 2H)
216		622.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 2H), 7.24 – 7.14 (m, 2H), 6.67 – 6.55 (m, 1H), 4.95 – 4.87 (m,2H), 4.82 – 4.75 (m, 2H), 4.64 – 4.56 (m, 1H), 4.05 – 3.94 (m, 1H), 3.93 – 3.50 (m, 6H), 3.40 – 3.08 (m, 5H), 2.92 (br t, J =12.0 Hz, 2H), 2.61 (s, 3H), 2.59 – 2.54 (m, 1H), 2.45 – 2.33 (m, 2H), 1.86 – 1.73 (m, 2H), 1.58 – 1.49 (m, 1H), 1.21 – 0.93 (m,8H).
217		636.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.24 – 7.17 (m, 2H), 6.67 – 6.54 (m, 1H), 4.67 – 4.57 (m,1H), 4.06 – 3.97 (m, 1H), 3.96 – 3.82 (m, 5H), 3.81 – 3.53 (m, 5H), 3.44 – 2.77 (m, 8H), 2.62 (s, 3H), 2.59 – 2.52 (m, 1H), 2.49-2.34 (m, 2H), 2.30 – 2.19 (m, 1H), 2.12 – 2.01 (m, 1H), 1.92 – 1.72 (m, 2H), 1.23 – 0.95 (m, 8H).
218		622.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 2H), 7.24 – 7.16 (m, 2H), 6.60 (s, 1H), 4.63 (d, J = 13.2 Hz, 1H),3.96 – 3.54 (m, 7H), 3.41 – 2.78 (m, 7H), 2.62 (s, 3H), 2.57 – 2.49 (m, 1H), 2.46 – 2.35 (m, 2H), 2.23 – 2.19 (m, 2H), 2.16 -2.05 (m, 1H), 1.86 – 1.70 (m, 3H), 1.18 – 1.02 (m, 7H), 0.97 (d, J = 6.4 Hz, 6H).
219		616.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.35 (m, 2H), 7.25 – 7.15 (m, 2H), 6.69 – 6.55 (m, 1H), 6.26 – 5.94 (m,1H), 4.51 (d, J = 13.2 Hz, 1H), 4.09 (d, J = 13.2 Hz, 1H), 3.96 – 3.54 (m, 5H), 3.52 – 3.15 (m, 4H), 3.13 – 2.87 (m, 2H), 2.84-2.64 (m, 2H), 2.62 (s, 3H), 2.59 – 2.37 (m, 2H), 1.92 – 1.80 (m, 2H), 1.75 – 1.67 (m, 1H), 1.32 – 0.93 (m, 8H).
221		650.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.60 – 7.50 (m, 1H), 7.40 – 7.29 (m, 2H), 6.70 (s, 1H), 4.60 (s, 4H), 4.53 (d, J = 13.2 Hz, 1H), 4.09 (d, J = 13.2 Hz, 1H), 3.97 (d, J = 11.2 Hz, 2H), 3.81 – 3.69 (m, 4H), 3.52 (t, J = 11.8 Hz, 3H), 3.11 (t, J = 12.2 Hz, 1H), 2.96 (ddd, J = 3.6, 8.0, 11.6 Hz, 2H), 2.63 (s, 3H), 2.50 (d, J = 6.8 Hz, 2H), 1.92 – 1.67 (m, 6H), 1.61 (d, J = 12.4 Hz, 2H), 1.39 – 1.26 (m, 1H), 1.23 – 0.92 (m, 8H).
222		595.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.59 – 7.50 (m, 1H), 7.39 – 7.29 (m, 2H), 6.69 (s, 1H), 4.60 (s, 2H), 3.99 (d, J = 13.6 Hz, 2H), 3.94 – 3.63 (m, 6H), 3.39 – 3.34 (m, 1H), 2.81 – 2.74 (m, 2H), 2.72 (s, 3H), 2.63 (s, 3H), 2.52 (d, J = 6.4 Hz, 2H), 2.06 (s, 2H), 1.75 (d, J = 12.8 Hz, 2H), 1.70 – 1.57 (m, 1H), 1.23 – 0.66 (m, 9H).
223		624.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.56 – 7.48 (m, 1H), 7.38 – 7.29 (m, 2H), 6.67 (s, 1H), 4.79 – 4.39 (m, 4H), 4.00 (d, J = 12.4 Hz, 1H), 3.96 – 3.66 (m, 6H), 3.65 (t, J = 6.4 Hz, 2H), 3.32 (s, 3H), 3.12 – 3.02 (m, 1H), 2.66 – 2.62 (m, 2H), 2.61 (s, 3H), 2.50 (d, J = 6.8 Hz, 2H), 2.04 (s, 1H), 1.87 – 1.74 (m, 2H), 1.73 – 1.63 (m, 1H), 1.43 – 0.64 (m, 10H).

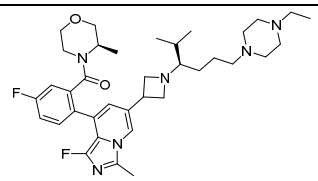
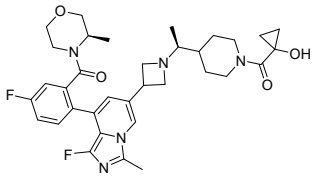
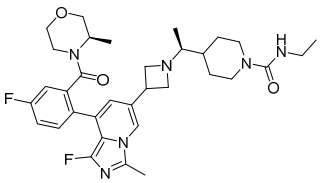
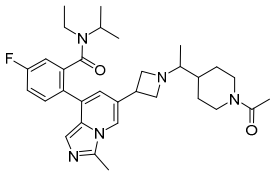
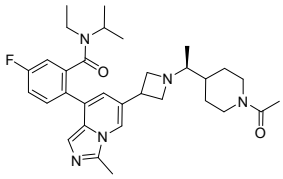
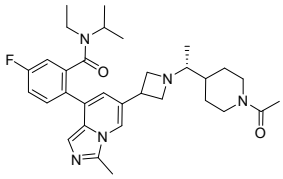
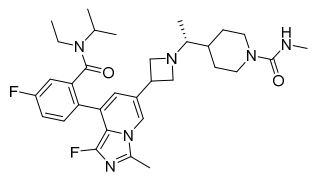
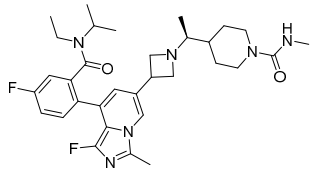
224		610.0	^{1}H NMR (400 MHz, CD_3OD) δ 7.98 – 7.81 (m, 1H), 7.57 – 7.47 (m, 1H), 7.38 – 7.26 (m, 2H), 6.79 – 6.45 (m, 1H), 4.58 (s, 2H), 4.48 (d, J = 12.8 Hz, 1H), 4.14 (q, J = 14.0 Hz, 3H), 3.92 – 3.72 (m, 7H), 3.41 – 3.36 (m, 4H), 3.08 – 2.92 (m, 2H), 2.66 – 2.59 (m, 3H), 2.57 (d, J = 6.4 Hz, 1H), 2.08 – 1.92 (m, 1H), 1.85 – 1.63 (m, 3H), 1.34 – 0.92 (m, 9H).
225		566.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.65 – 7.47 (m, 1H), 7.45 – 7.24 (m, 2H), 6.86 – 6.51 (m, 1H), 4.47 – 3.39 (m, 9H), 3.16 – 2.80 (m, 5H), 2.58 – 2.52 (m, 3H), 2.49 – 2.42 (m, 2H), 2.34 – 2.26 (m, 2H), 2.00 – 1.91 (m, 3H), 1.78 – 1.58 (m, 2H), 1.56 – 1.44 (m, 1H), 1.24 – 0.62 (m, 5H).
226		605.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.57 – 7.49 (m, 1H), 7.38 – 7.29 (m, 2H), 6.74 – 6.64 (m, 1H), 4.52 – 4.41 (m, 1H), 3.97 – 3.59 (m, 7H), 3.30 – 3.22 (m, 5H), 3.15 – 3.07 (m, 1H), 2.95 – 2.79 (m, 1H), 2.72 – 2.65 (m, 1H), 2.63 – 2.58 (m, 3H), 2.51 – 2.43 (m, 2H), 1.87 – 1.75 (m, 2H), 1.73 – 1.62 (m, 1H), 1.33 – 0.74 (m, 9H).
227		636.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.54 – 7.48 (m, 1H), 7.46 – 7.36 (m, 2H), 6.68 – 6.53 (m, 1H), 4.37 – 4.30 (m, 1H), 3.98 – 3.78 (m, 3H), 3.70 – 3.62 (m, 5H), 3.36 – 3.25 (m, 3H), 3.19 – 3.11 (m, 3H), 2.99 – 2.93 (m, 1H), 2.56 – 2.53 (m, 3H), 2.35 – 2.31 (m, 2H), 2.08 – 1.93 (m, 4H), 1.76 – 1.46 (m, 4H), 1.12 – 0.74 (m, 9H).
229		553.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.52 – 7.45 (m, 1H), 7.43 – 7.36 (m, 2H), 6.35 – 6.22 (m, 1H), 3.83 – 3.75 (m, 3H), 3.40 – 3.33 (m, 3H), 3.28 – 3.19 (m, 4H), 2.96 – 2.89 (m, 2H), 2.73 – 2.66 (m, 3H), 2.56 – 2.52 (m, 3H), 2.34 – 2.29 (m, 2H), 2.10 – 2.03 (m, 1H), 1.57 – 1.47 (m, 3H), 1.18 – 0.72 (m, 9H).
231		594.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 – 8.38 (m, 1H), 8.20 – 7.78 (m, 1H), 7.68 – 7.16 (m, 3H), 6.92 – 6.40 (m, 1H), 4.70 – 3.39 (m, 11H), 2.96 (s, 11H), 2.12 – 1.67 (m, 3H), 1.10 (s, 11H).
233		633.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.05 (s, 1H), 7.56 – 7.35 (m, 4H), 6.79 – 6.52 (m, 1H), 4.26 – 4.17 (m, 1H), 4.12 (d, J = 13.2 Hz, 2H), 4.05 – 3.79 (m, 4H), 3.73 – 3.60 (m, 2H), 3.09 (q, J = 7.4 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.65 (t, J = 12.6 Hz, 3H), 2.57 (s, 3H), 1.77 – 1.69 (m, 1H), 1.63 (d, J = 12.4 Hz, 2H), 1.25 – 1.15 (m, 3H), 1.14 – 0.96 (m, 6H).
234		644.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.85 (s, 2H), 7.88 (s, 1H), 7.55 – 7.47 (m, 1H), 7.43 – 7.37 (m, 2H), 6.76 – 6.47 (m, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.54 (s, 4H), 3.49 (s, 1H), 3.14 – 3.03 (m, 4H), 2.78 (t, J = 12.0 Hz, 1H), 2.55 (s, 3H), 2.33 (d, J = 6.4 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.72 – 1.51 (m, 3H), 1.25 – 0.88 (m, 9H).

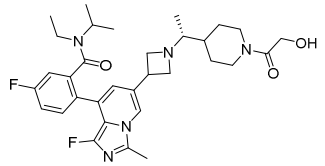
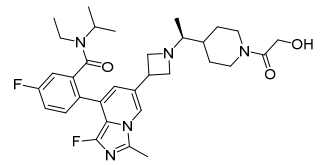
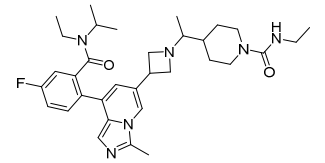
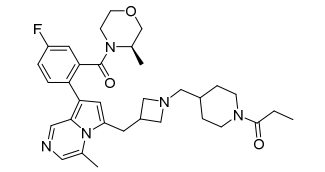
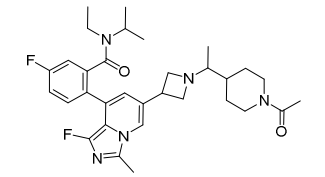
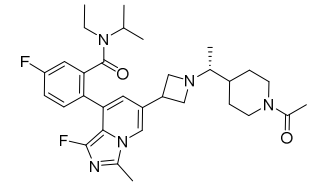
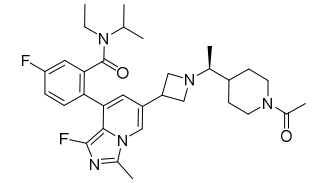
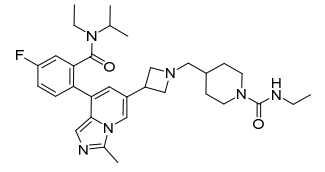
235		525.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 10.4 Hz, 1H), 7.64 – 7.49 (m, 1H), 7.38 – 7.17 (m, 2H), 6.88 – 6.59 (m, 1H), 4.64 – 4.33 (m, 1H), 4.10 – 3.88 (m, 1H), 3.85 – 3.77 (m, 1H), 3.76 – 3.66 (m, 3H), 3.63 – 3.53 (m, 1H), 3.44 – 3.33 (m, 2H), 3.29 – 3.10 (m, 4H), 3.08 – 2.65 (m, 2H), 2.59 (s, 3H), 2.51 – 2.35 (m, 2H), 2.33 – 1.93 (m, 1H), 1.92 – 1.79 (m, 1H), 1.75 – 1.51 (m, 3H), 1.37 – 1.07 (m, 3H), 0.86 – 0.55 (m, 1H).
236		555.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.78 (m, 1H), 7.65 – 7.47 (m, 1H), 7.44 – 7.25 (m, 2H), 6.82 – 6.49 (m, 1H), 4.38 – 3.44 (m, 10H), 3.40 – 2.64 (m, 11H), 2.55 (s, 3H), 1.64 – 1.43 (m, 4H), 1.27 – 0.49 (m, 3H).
239		541.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.67 – 7.49 (m, 1H), 7.41 – 7.16 (m, 2H), 7.10 – 6.73 (m, 1H), 4.63 – 4.06 (m, 2H), 3.83 – 3.53 (m, 9H), 3.38 – 3.33 (m, 2H), 3.19 – 2.87 (m, 2H), 2.64 – 2.51 (m, 5H), 2.28 – 1.86 (m, 1H), 1.71 – 1.59 (m, 2H), 1.56 – 1.46 (m, 2H), 1.35 – 1.25 (m, 1H), 1.24 – 1.09 (m, 1H), 0.85 – 0.56 (m, 1H).
240		511.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.77 (m, 1H), 7.66 – 7.47 (m, 1H), 7.44 – 7.22 (m, 2H), 6.83 – 6.45 (m, 1H), 4.43 – 3.89 (m, 1H), 3.79 – 3.46 (m, 8H), 3.32 – 3.28 (m, 3H), 3.16 – 2.78 (m, 4H), 2.58 – 2.52 (m, 3H), 2.45 – 2.36 (m, 2H), 2.20 – 2.07 (m, 1H), 1.98 – 1.85 (m, 1H), 1.56 – 1.43 (m, 1H), 1.27 – 0.64 (m, 3H).
242		657.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.55 – 7.36 (m, 3H), 6.60 (s, 1H), 4.28 (t, J = 12.8 Hz, 4H), 3.80 – 3.42 (m, 8H), 3.23 – 3.03 (m, 4H), 2.81 – 2.63 (m, 3H), 2.55 (s, 3H), 2.34 – 2.26 (m, 2H), 1.72 – 1.59 (m, 2H), 1.52 – 1.36 (m, 1H), 1.15 – 0.67 (m, 8H).
246		595.0	^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 9.2 Hz, 1H), 7.55 – 7.41 (m, 1H), 7.26 – 7.07 (m, 2H), 6.81 – 6.51 (m, 1H), 4.49 (s, 2H), 4.41 – 4.20 (m, 1H), 3.72 – 3.64 (m, 3H), 3.59 – 3.49 (m, 3H), 2.72 (s, 6H), 2.70 (d, J = 2.4 Hz, 1H), 2.68 – 2.61 (m, 2H), 2.50 (s, 3H), 2.44 (d, J = 6.8 Hz, 2H), 1.69 – 1.61 (m, 2H), 1.54 – 1.48 (m, 1H), 1.29 – 1.25 (m, 1H), 1.19 (s, 2H), 1.16 – 1.04 (m, 4H), 0.82 – 0.74 (m, 1H), 0.73 – 0.65 (m, 1H).
247		632.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 1H), 7.58 – 7.48 (m, 1H), 7.39 – 7.27 (m, 2H), 6.92 – 6.60 (m, 1H), 4.06 – 3.97 (m, 2H), 3.91 – 3.80 (m, 2H), 3.68 – 3.59 (m, 2H), 2.77 (d, J = 5.6 Hz, 2H), 2.62 (s, 3H), 2.52 – 1.95 (m, 2H), 1.89 – 1.79 (m, 3H), 1.64 – 1.51 (m, 1H), 1.40 – 1.19 (m, 11H), 1.16 – 1.08 (m, 2H), 1.02 – 0.96 (m, 1H), 0.93 – 0.81 (m, 3H).

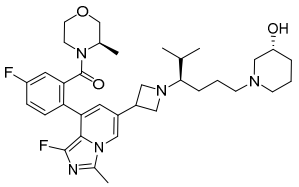
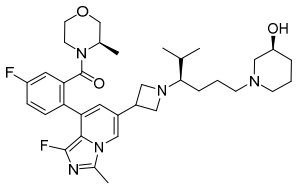
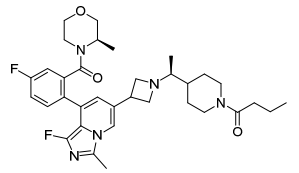
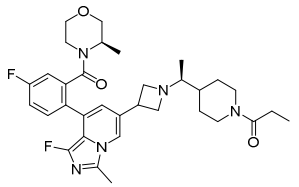
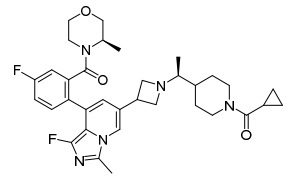
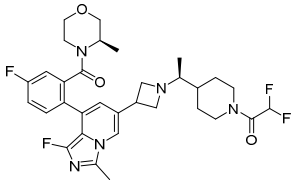
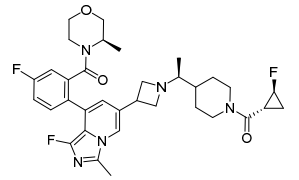
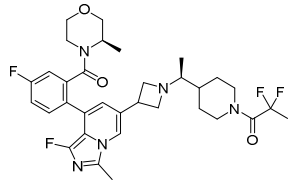
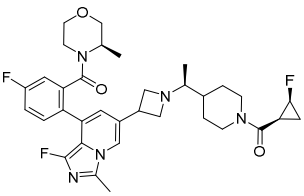
248		608.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.64 – 7.48 (m, 1H), 7.44 – 7.25 (m, 2H), 6.83 – 6.52 (m, 1H), 6.26 – 6.17 (m, 1H), 4.47 – 3.87 (m, 3H), 3.79 – 3.48 (m, 5H), 3.28 – 2.64 (m, 7H), 2.56 – 2.52 (m, 3H), 2.34 – 2.27 (m, 2H), 1.78 – 1.61 (m, 2H), 1.58 – 1.47 (m, 1H), 1.26 – 0.51 (m, 10H).
249		591.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.79 (m, 1H), 7.62 – 7.47 (m, 1H), 7.44 – 7.25 (m, 2H), 6.89 – 6.50 (m, 1H), 4.32 – 3.92 (m, 4H), 3.77 – 3.48 (m, 6H), 3.15 – 3.05 (m, 2H), 3.03 – 2.89 (m, 2H), 2.69 – 2.53 (m, 6H), 2.34 – 2.28 (m, 2H), 1.79 – 1.62 (m, 2H), 1.58 – 1.44 (m, 1H), 1.28 – 0.87 (m, 5H), 0.81 – 0.53 (m, 1H).
250		581.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.65 – 7.45 (m, 1H), 7.44 – 7.25 (m, 2H), 6.83 – 6.49 (m, 1H), 6.35 – 6.21 (m, 1H), 4.45 – 3.38 (m, 8H), 3.22 – 2.75 (m, 5H), 2.62 – 2.51 (m, 9H), 2.32 – 2.25 (m, 2H), 1.72 – 1.52 (m, 2H), 1.47 – 1.33 (m, 1H), 1.26 – 0.85 (m, 4H), 0.82 – 0.56 (m, 1H).
251		616.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.63 – 7.48 (m, 1H), 7.45 – 7.27 (m, 2H), 6.83 – 6.49 (m, 1H), 4.36 – 3.88 (m, 1H), 3.72 – 3.51 (m, 6H), 3.32 – 3.20 (m, 5H), 3.15 – 3.05 (m, 2H), 3.03 – 2.97 (m, 2H), 2.79 – 2.70 (m, 2H), 2.57 – 2.52 (m, 3H), 2.36 – 2.29 (m, 2H), 1.86 – 1.68 (m, 2H), 1.45 – 1.34 (m, 1H), 1.23 – 1.04 (m, 7H), 0.81 – 0.60 (m, 1H).
252		628.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.63 – 7.47 (m, 1H), 7.46 – 7.19 (m, 2H), 6.84 – 6.47 (m, 1H), 4.41 – 3.88 (m, 1H), 3.75 – 3.49 (m, 6H), 3.33 – 3.30 (m, 6H), 3.16 – 3.04 (m, 2H), 2.82 – 2.72 (m, 2H), 2.56 – 2.53 (m, 3H), 2.38 – 2.28 (m, 2H), 1.89 – 1.68 (m, 2H), 1.49 – 1.33 (m, 1H), 1.28 – 0.84 (m, 8H), 0.78 – 0.51 (m, 1H).
253		590.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.03 – 7.73 (m, 2H), 7.65 – 7.23 (m, 3H), 6.91 – 6.46 (m, 1H), 4.47 – 3.39 (m, 8H), 3.28 – 2.76 (m, 5H), 2.56 (s, 3H), 2.32 (d, J = 6.8 Hz, 2H), 2.08 – 1.64 (m, 6H), 1.43 – 0.97 (m, 5H), 0.86 – 0.57 (m, 1H).
254		617.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.76 (m, 1H), 7.64 – 7.23 (m, 3H), 6.85 – 6.49 (m, 1H), 4.42 – 3.35 (m, 9H), 3.30 – 2.74 (m, 7H), 2.55 (s, 3H), 2.38 – 2.28 (m, 2H), 1.89 – 1.67 (m, 2H), 1.64 – 1.51 (m, 3H), 1.48 – 1.38 (m, 2H), 1.22 – 0.54 (m, 5H).
256		551.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.46 (m, 2H), 7.26 – 7.10 (m, 3H), 7.01 – 6.70 (m, 1H), 4.63 – 4.09 (m,1H), 4.05 – 3.93 (m, 2H), 3.84 – 3.44 (m, 5H), 3.42 – 2.88 (m, 10H), 2.69 (s, 3H), 2.48 – 2.28 (m, 1H), 1.94 – 1.77 (m, 1H),1.67 – 1.41 (m, 7H), 1.33 – 1.26 (m, 1H), 1.17 – 1.03 (m, 1H), 0.81 – 0.40 (m, 1H).

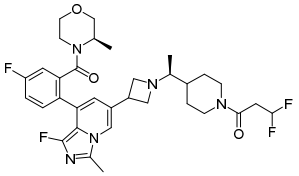
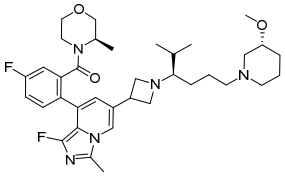
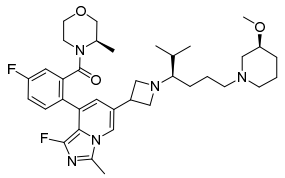
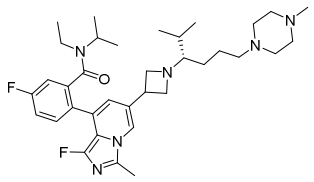
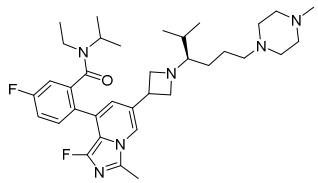
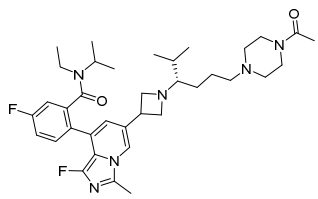
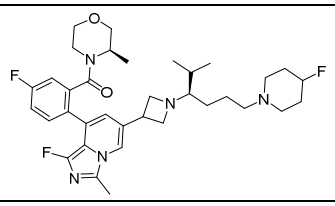
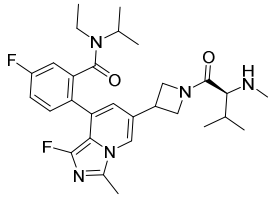
258		643.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.79 (m, 1H), 7.63 – 7.24 (m, 3H), 6.83 – 6.49 (m, 1H), 4.28 (t, J = 13.2 Hz, 4H), 3.84 – 3.41 (m, 9H), 3.16 – 2.64 (m, 7H), 2.54 (s, 3H), 2.34 – 2.27 (m, 2H), 1.75 – 1.59 (m, 2H), 1.52 – 1.39 (m, 1H), 1.21 – 0.62 (m, 5H).
259		582.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.77 (m, 1H), 7.62 – 7.47 (m, 1H), 7.43 – 7.25 (m, 2H), 6.84 – 6.50 (m, 1H), 4.37 – 3.69 (m, 4H), 3.61 – 3.46 (m, 8H), 3.16 – 3.02 (m, 4H), 2.81 – 2.63 (m, 3H), 2.56 – 2.53 (m, 3H), 2.32 – 2.28 (m, 2H), 1.78 – 1.58 (m, 2H), 1.51 – 1.39 (m, 1H), 1.25 – 1.04 (m, 2H), 1.03 – 0.91 (m, 2H), 0.80 – 0.55 (m, 1H).
261		595.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 10.8 Hz, 1H), 7.65 – 7.52 (m, 1H), 7.38 – 7.17 (m, 2H), 6.87 – 6.60 (m, 1H), 4.63 – 4.33 (m, 1H), 4.13 – 3.53 (m, 8H), 3.32 (s, 2H), 3.23 (s, 2H), 3.17 (q, J = 7.4 Hz, 2H), 3.05 – 2.86 (m, 1H), 2.78 – 2.71 (m, 2H), 2.60 (s, 3H), 2.47 (d, J = 6.4 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.61 (tdd, J = 3.6, 7.2, 10.8 Hz, 1H), 1.30 (d, J = 6.4 Hz, 1H), 1.22 – 1.05 (m, 6H), 0.80 (d, J = 5.2 Hz, 1H).
262		622.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.67 – 7.46 (m, 1H), 7.44 – 7.16 (m, 2H), 6.90 – 6.43 (m, 1H), 4.57 – 4.05 (m, 3H), 4.03 – 3.62 (m, 1H), 3.36 (s, 5H), 3.18 (s, 3H), 3.15 – 2.61 (m, 6H), 2.55 (s, 3H), 2.39 – 2.25 (m, 2H), 1.85 – 1.65 (m, 2H), 1.63 – 1.46 (m, 1H), 1.35 – 0.48 (m, 10H).
263-1		605.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 14.0 Hz, 1H), 7.68 – 7.52 (m, 1H), 7.40 – 7.17 (m, 2H), 6.97 – 6.67 (m, 1H), 4.65 – 4.52 (m, 2H), 3.86 – 3.74 (m, 3H), 3.73 – 3.57 (m, 3H), 3.32 – 2.88 (m, 7H), 2.78 – 2.56 (m, 5H), 2.45 (s, 1H), 2.21 – 1.93 (m, 1H), 1.77 (s, 2H), 1.67 – 1.55 (m, 1H), 1.38 – 1.16 (m, 4H), 0.92 (d, J = 5.6 Hz, 3H), 0.86 – 0.77 (m, 1H).
263-2		605.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 – 7.74 (m, 1H), 7.65 – 7.50 (m, 1H), 7.39 – 7.16 (m, 2H), 6.93 – 6.58 (m, 1H), 4.63 – 4.32 (m, 2H), 3.86 – 3.54 (m, 6H), 3.31 (s, 2H), 3.27 – 2.88 (m, 5H), 2.81 – 2.63 (m, 1H), 2.60 (s, 4H), 2.39 (s, 1H), 2.27 – 1.94 (m, 1H), 1.74 (s, 2H), 1.67 – 1.51 (m, 1H), 1.47 – 1.11 (m, 4H), 0.88 (d, J = 6.0 Hz, 3H), 0.83 – 0.55 (m, 1H).
264-1		595.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 12.2 Hz, 1H), 7.65 – 7.50 (m, 1H), 7.38 – 7.14 (m, 2H), 6.91 – 6.56 (m, 1H), 4.69 – 4.21 (m, 2H), 4.04 (t, J = 12.0 Hz, 2H), 3.85 – 3.52 (m, 5H), 3.40 – 3.31 (m, 2H), 3.27 – 3.17 (m, 2H), 3.05 – 2.86 (m, 1H), 2.79 – 2.72 (m, 1H), 2.70 (s, 3H), 2.69 – 2.64 (m, 1H), 2.60 (s, 3H), 2.44 – 2.31 (m, 1H), 1.74 – 1.60 (m, 2H), 1.59 – 1.44 (m, 1H), 1.34 – 1.12 (m, 4H), 0.88 (d, J = 6.0 Hz, 3H), 0.83 – 0.75 (m, 1H).
264-2		595.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 11.6 Hz, 1H), 7.64 – 7.48 (m, 1H), 7.39 – 7.15 (m, 2H), 6.88 – 6.56 (m, 1H), 4.68 – 4.31 (m, 2H), 4.05 (t, J = 12.2 Hz, 2H), 3.81 – 3.53 (m, 5H), 3.40 – 3.31 (m, 2H), 3.27 – 3.21 (m, 1H), 3.20 – 3.14 (m, 1H), 3.06 – 2.88 (m, 1H), 2.80 – 2.73 (m, 1H), 2.71 (s, 3H), 2.69 – 2.64 (m, 1H), 2.60 (s, 3H), 2.37 (s, 1H), 1.70 – 1.60 (m, 2H), 1.58 – 1.45 (m, 1H), 1.33 –

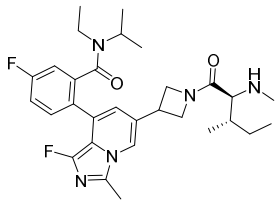
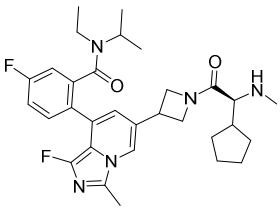
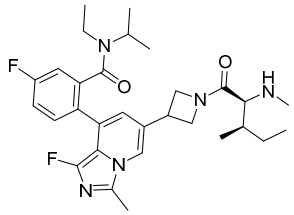
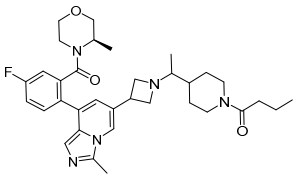
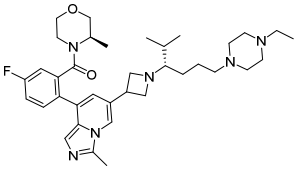
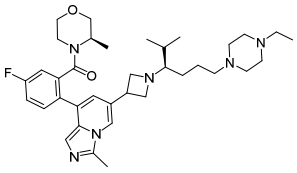
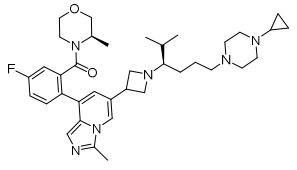
			1.13 (m, 4H), 0.87 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 4.4 Hz, 1H).
265		651.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.87 – 7.72 (m, 1H), 7.66 – 7.51 (m, 1H), 7.50 – 7.14 (m, 3H), 6.89 – 6.56 (m, 1H), 4.58 (s, 3H), 3.81 – 3.52 (m, 9H), 3.29 – 3.22 (m, 2H), 2.60 (s, 3H), 2.52 – 2.35 (m, 6H), 2.33 – 2.24 (m, 1H), 2.08 (s, 3H), 1.87 (s, 1H), 1.60 (s, 2H), 1.47 – 1.37 (m, 1H), 1.36 – 1.24 (m, 3H), 1.21 – 1.12 (m, 1H), 0.98 – 0.89 (m, 6H), 0.86 – 0.75 (m, 1H).
268		602.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.77 (m, 1H), 7.65 – 7.24 (m, 3H), 6.92 – 6.50 (m, 2H), 4.43 – 3.34 (m, 9H), 3.27 – 2.64 (m, 7H), 2.54 (s, 3H), 2.36 – 2.27 (m, 2H), 1.89 – 1.50 (m, 3H), 1.22 – 0.52 (m, 5H).
269		592.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.72 (m, 1H), 7.66 – 7.18 (m, 3H), 6.93 – 6.44 (m, 1H), 4.48 – 3.35 (m, 9H), 3.29 – 2.73 (m, 7H), 2.55 (s, 3H), 2.37 – 2.26 (m, 2H), 1.99 – 1.47 (m, 4H), 1.22 – 0.52 (m, 9H).
270		596.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.92 – 7.75 (m, 1H), 7.68 – 7.49 (m, 1H), 7.44 – 7.14 (m, 2H), 6.92 – 6.59 (m, 1H), 4.72 – 4.34 (m, 3H), 4.14 – 4.06 (m, 4H), 3.84 – 3.48 (m, 5H), 3.28 – 2.97 (m, 3H), 2.91 – 2.66 (m, 3H), 2.60 (s, 3H), 2.54 – 2.42 (m, 2H), 1.81 – 1.55 (m, 3H), 1.37 – 1.03 (m, 7H), 0.85 – 0.56 (m, 1H).
271		608.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.63 – 7.48 (m, 1H), 7.45 – 7.21 (m, 2H), 6.84 – 6.50 (m, 1H), 4.45 – 3.36 (m, 9H), 3.18 – 2.75 (m, 5H), 2.54 (s, 3H), 2.48 – 2.43 (m, 1H), 2.30 (d, J = 6.8 Hz, 2H), 2.15 (d, J = 6.8 Hz, 2H), 2.02 – 1.86 (m, 1H), 1.81 – 1.60 (m, 2H), 1.58 – 1.42 (m, 1H), 1.26 – 0.50 (m, 12H).
272		622.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.79 (m, 1H), 7.62 – 7.49 (m, 1H), 7.45 – 7.25 (m, 2H), 6.81 – 6.49 (m, 1H), 4.40 – 3.45 (m, 14H), 3.17 – 2.74 (m, 6H), 2.56 – 2.53 (m, 3H), 2.34 – 2.28 (m, 2H), 2.02 – 1.92 (m, 2H), 1.80 – 1.63 (m, 2H), 1.59 – 1.44 (m, 1H), 1.27 – 0.53 (m, 6H).
273		602.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.75 (m, 1H), 7.63 – 7.49 (m, 1H), 7.46 – 7.25 (m, 2H), 6.83 – 6.50 (m, 1H), 4.45 – 3.37 (m, 9H), 3.31 – 3.24 (m, 2H), 3.16 – 2.96 (m, 3H), 2.84 – 2.80 (m, 3H), 2.69 – 2.61 (m, 2H), 2.57 – 2.52 (m, 3H), 2.37 – 2.30 (m, 2H), 1.89 – 1.69 (m, 2H), 1.45 – 1.30 (m, 1H), 1.26 – 1.00 (m, 4H), 0.83 – 0.55 (m, 1H).
274		550.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.94 (m, 1H), 7.58 – 7.49 (m, 1H), 7.41 – 7.28 (m, 2H), 6.66 – 6.48 (m, 1H), 4.70 – 4.46 (m, 1H), 4.34 – 4.12 (m, 2H), 4.02 – 3.76 (m, 2H), 3.52 – 3.36 (m, 1H), 3.29 – 2.65 (m, 5H), 2.56 – 2.53 (m, 3H), 2.37 – 2.26 (m, 1H), 1.82 – 1.19 (m, 7H), 1.04 – 0.72 (m, 7H), 0.47 – 0.31 (m, 2H).

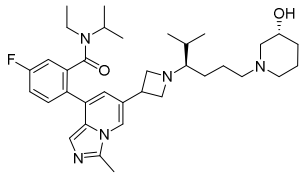
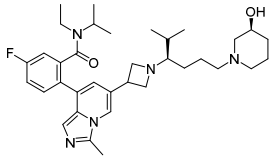
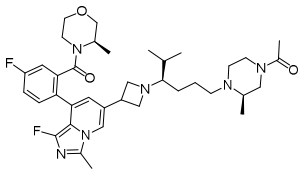
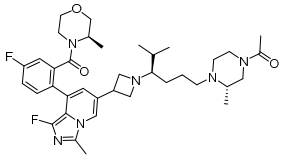
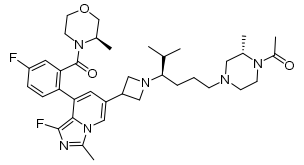
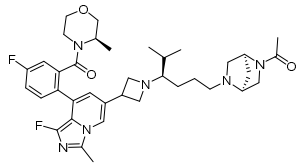
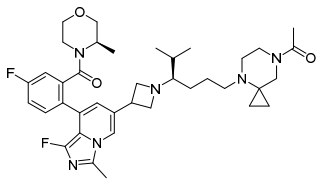
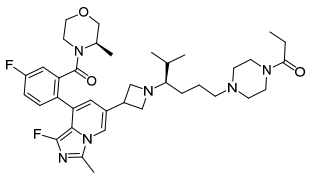
277		637.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.31 (m, 2H), 7.25 – 7.04 (m, 2H), 6.81 – 6.49 (m, 1H), 4.68 – 4.10 (m,1H), 3.81 – 2.69 (m, 11H), 2.61 (s, 3H), 2.55 – 1.93 (m, 12H), 1.88 – 1.74 (m, 1H), 1.64 – 1.39 (m, 3H), 1.38 – 0.53 (m, 14H).
278		622.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.78 (m, 1H), 7.66 – 7.21 (m, 3H), 6.90 – 6.43 (m, 1H), 6.29 – 6.16 (m, 1H), 4.66 – 3.37 (m, 9H), 3.25 – 2.71 (m, 6H), 2.57 – 2.52 (m, 3H), 2.24 – 2.15 (m, 1H), 1.76 – 1.39 (m, 3H), 1.28 – 0.98 (m, 4H), 0.92 – 0.46 (m, 9H).
279		609.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.79 (m, 1H), 7.61 – 7.26 (m, 3H), 6.87 – 6.42 (m, 1H), 6.38 – 6.30 (m, 1H), 4.41 – 3.63 (m, 4H), 3.62 – 3.38 (m, 5H), 3.31 – 2.74 (m, 9H), 2.57 – 2.53 (m, 3H), 2.22 – 2.13 (m, 1H), 1.64 – 1.31 (m, 3H), 1.25 – 1.04 (m, 3H), 1.02 – 0.92 (m, 4H), 0.77 – 0.54 (m, 4H).
281		548.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.89 (m, 1H), 7.73 – 7.63 (m, 1H), 7.43 – 7.26 (m, 2H), 7.08 – 6.99 (m, 1H), 6.87 – 6.66 (m, 1H), 4.50 – 4.38 (m, 1H), 3.83 (d, J = 12.4 Hz, 1H), 3.60 – 3.39 (m, 4H), 3.19 – 2.65 (m, 5H), 2.64 – 2.55 (m, 3H), 2.44 – 2.29 (m, 1H), 2.24 – 2.15 (m, 1H), 1.97 (s, 3H), 1.77 – 1.39 (m, 3H), 1.27 – 1.01 (m, 2H), 0.95 – 0.68 (m, 10H), 0.30 – 0.23 (m, 2H).
281-1		548.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.75 – 7.61 (m, 1H), 7.47 – 7.23 (m, 2H), 7.04 (s, 1H), 6.93 – 6.65 (m, 1H), 4.51 – 4.18 (m, 1H), 3.94 – 3.75 (m, 1H), 3.61 – 3.42 (m, 4H), 3.21 – 2.74 (m, 5H), 2.60 (s, 3H), 2.45 – 2.30 (m, 1H), 2.21 (s, 1H), 1.98 (s, 3H), 1.79 – 1.39 (m, 3H), 1.29 – 0.70 (m, 12H), 0.27 (s, 2H).
281-2		548.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.68 (s, 1H), 7.51 – 7.18 (m, 2H), 7.03 (s, 1H), 6.94 – 6.62 (m, 1H), 4.54 – 4.21 (m, 1H), 3.93 – 3.75 (m, 1H), 3.50 (s, 4H), 3.22 – 2.77 (m, 5H), 2.66 – 2.54 (m, 3H), 2.45 – 2.32 (m, 1H), 2.20 (s, 1H), 1.97 (s, 3H), 1.74 – 1.38 (m, 3H), 1.23 – 1.03 (m, 2H), 0.99 – 0.63 (m, 10H), 0.27 (s, 2H).
283-1		581.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.81 – 7.74 (m, 1H), 7.59 – 7.52 (m, 1H), 7.30 (dt, J = 2.6, 8.4 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.59 (s, 1H), 4.05 (t, J = 11.8 Hz, 2H), 3.75 – 3.67 (m, 2H), 3.67 – 3.52 (m, 2H), 3.51 – 3.38 (m, 1H), 3.28 – 3.12 (m, 2H), 3.10 – 2.97 (m, 1H), 2.81 – 2.73 (m, 1H), 2.71 (s, 3H), 2.69 – 2.63 (m, 1H), 2.58 (s, 3H), 2.43 – 2.32 (m, 1H), 1.71 – 1.61 (m, 2H), 1.52 (t, J = 14.4 Hz, 1H), 1.34 – 1.09 (m, 3H), 1.00 (d, J = 6.4 Hz, 2H), 0.96 – 0.85 (m, 6H), 0.43 (d, J = 5.2 Hz, 2H).
283-2		581.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 – 7.80 (m, 1H), 7.56 – 7.48 (m, 1H), 7.39 – 7.25 (m, 2H), 6.73 – 6.55 (m, 1H), 6.33 -6.26 (m, 1H), 4.28 – 3.89 (m, 2H), 3.58 – 3.40 (m, 4H), 3.13 – 2.56 (m, 5H), 2.55 – 2.52 (m, 6H), 2.26 – 2.10 (m, 1H), 1.67 -1.30 (m, 3H), 1.16 – 0.68 (m, 13H), 0.39 (br s, 2H).

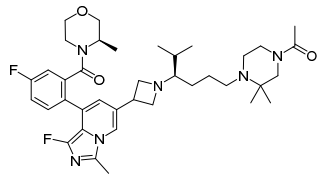
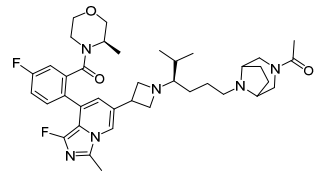
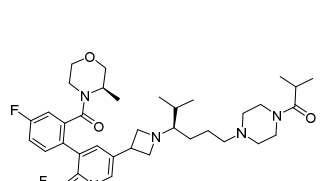
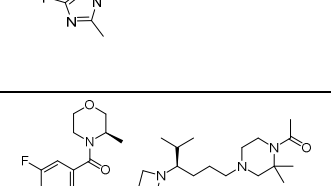
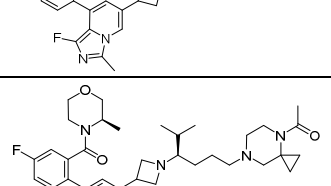
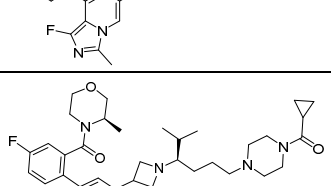
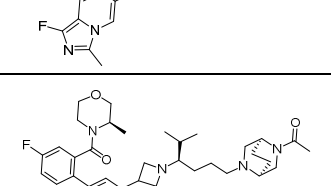
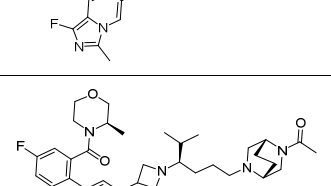
284-1		582.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 – 7.74 (m, 1H), 7.62 – 7.49 (m, 1H), 7.31 (dt, J = 2.0, 8.4 Hz, 1H), 7.26 – 7.16 (m, 1H), 6.75 (d, J = 14.0 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.32 – 4.12 (m, 2H), 3.89 – 3.72 (m, 3H), 3.71 – 3.54 (m, 2H), 3.52 – 3.40 (m, 1H), 3.31 – 3.18 (m, 2H), 3.11 – 2.90 (m, 2H), 2.76 – 2.61 (m, 1H), 2.59 (s, 3H), 2.52 – 2.40 (m, 1H), 1.84 – 1.68 (m, 2H), 1.66 – 1.52 (m, 1H), 1.42 – 1.10 (m, 3H), 1.04 – 0.81 (m, 9H), 0.43 (d, J = 6.0 Hz, 2H).
284-2		582.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 – 7.77 (m, 1H), 7.58 – 7.47 (m, 1H), 7.40 – 7.23 (m, 2H), 6.78 – 6.53 (m, 1H), 4.46 -4.20 (m, 2H), 4.13 – 3.97 (m, 2H), 3.83 – 3.55 (m, 2H), 3.53 – 3.43 (m, 4H), 3.13 – 3.03 (m, 2H), 2.96 – 2.80 (m, 2H), 2.53 (s,3H), 2.47 – 2.34 (m, 1H), 2.25 – 2.15 (m, 1H), 1.77 – 1.39 (m, 3H), 1.26 – 0.72 (m, 12H), 0.46 – 0.31 (m, 2H).
285		577.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.91 (m, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.06 – 7.00 (m, 1H), 6.83 – 6.70 (m, 1H), 6.37 – 6.30 (m, 1H), 4.00 (d, J = 11.2 Hz, 2H), 3.57 – 3.32 (m, 5H), 3.13 – 2.88 (m, 5H), 2.61 – 2.52 (m, 4H), 2.46 (s, 1H), 2.23 – 2.13 (m, 1H), 1.68 – 1.34 (m, 3H), 1.18 – 0.85 (m, 9H), 0.82 – 0.72 (m, 6H), 0.27 (dd, J = 2.8, 6.4 Hz, 2H).
287		576.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 – 8.38 (m, 1H), 7.64 – 7.44 (m, 1H), 7.39 – 7.17 (m, 3H), 6.62 – 6.51 (m, 1H), 4.37 – 3.88 (m, 2H), 3.83 – 3.35 (m, 8H), 3.13 – 2.66 (m, 10H), 2.31 – 2.20 (m, 4H), 1.80 – 1.37 (m, 4H), 1.26 – 1.13 (m, 1H), 1.06 – 0.85 (m, 6H), 0.63 – 0.29 (m, 1H).
288		566.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.57 – 7.47 (m, 1H), 7.39 – 7.26 (m, 2H), 6.75 – 6.54 (m, 1H), 4.51 – 4.18 (m, 1H), 3.88 – 3.76 (m, 1H), 3.58 – 3.38 (m, 4H), 3.26 – 2.57 (m, 5H), 2.53 (s, 3H), 2.45 – 2.29 (m, 1H), 2.18 (s, 1H), 1.96 (s, 3H), 1.77 – 1.34 (m, 3H), 1.27 – 1.01 (m, 2H), 0.99 – 0.65 (m, 10H), 0.39 (s, 2H).
288-1		566.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.82 – 7.74 (m, 1H), 7.60 – 7.50 (m, 1H), 7.30 (dt, J = 2.4, 8.4 Hz, 1H), 7.25 – 7.18 (m, 1H), 6.75 (br d, J = 14.4 Hz, 1H), 4.60 (d, J = 11.6 Hz, 2H), 3.97 (d, J = 13.2 Hz, 1H), 3.78 – 3.69 (m, 2H), 3.68 – 3.55 (m, 2H), 3.52 – 3.40 (m, 1H), 3.29 – 2.99 (m, 4H), 2.59 (s, 3H), 2.42 (s, 1H), 2.09 (s, 3H), 1.81 – 1.65 (m, 2H), 1.65 – 1.50 (m, 1H), 1.41 – 1.05 (m, 4H), 1.00 (d, J = 6.4 Hz, 2H), 0.96 – 0.81 (m, 6H), 0.43 (d, J = 5.6 Hz, 2H).
288-2		566.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.75 (m, 1H), 7.58 – 7.25 (m, 3H), 6.79 – 6.54 (m, 1H), 4.51 – 4.18 (m, 1H), 3.89 -3.40 (m, 5H), 3.12 – 2.80 (m, 4H), 2.53 (s, 3H), 2.47 – 2.07 (m, 3H), 1.96 (s, 3H), 1.79 – 1.37 (m, 3H), 1.30 – 0.65 (m, 12H),0.50 – 0.29 (m, 2H).
290		563.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 1H), 7.57 – 7.47 (m, 1H), 7.23 – 7.07 (m, 3H), 6.95 – 6.81 (m, 1H),4.55 – 4.32 (m, 1H), 3.92 (br d, J = 12.0 Hz, 2H), 3.72 – 3.41 (m, 4H), 3.33 – 3.05 (m, 4H), 3.00 – 2.84 (m, 1H), 2.75 (br t, J =12.8 Hz, 2H), 2.67 (s, 3H), 2.46 – 2.33 (m, 2H), 1.81 – 1.70 (m, 2H), 1.62 – 1.19 (m, 3H), 1.14 (br t, J = 7.2 Hz, 5H), 1.00 -0.74 (m, 6H), 0.26 (m, 2H).

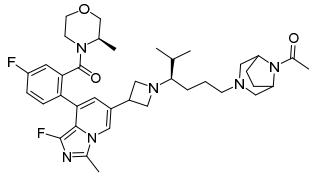
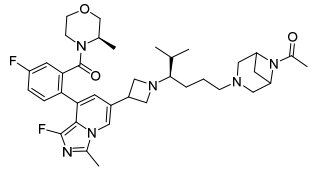
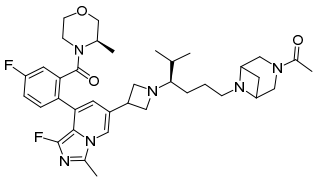
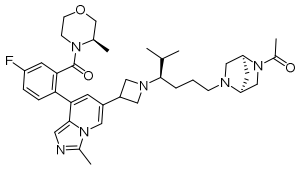
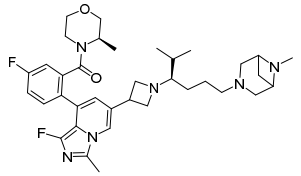
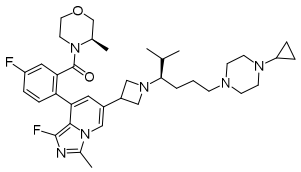
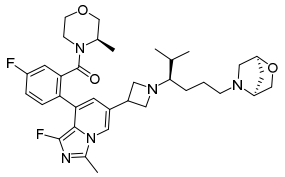
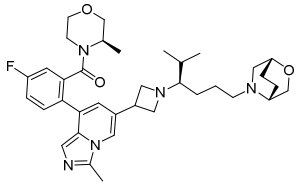
292		624.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.34 (m, 2H), 7.25 – 7.06 (m, 2H), 6.84 – 6.49 (m, 1H), 4.70 – 4.07 (m,1H), 3.93 – 2.69 (m, 12H), 2.62 (s, 3H), 2.57 – 1.87 (m, 8H), 1.74 – 1.08 (m, 11H), 0.95 – 0.55 (m, 7H).
293		624.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.75 (m, 1H), 7.67 – 7.18 (m, 3H), 6.84 – 6.41 (m, 1H), 4.51 (d, J = 4.8 Hz, 1H), 4.41 – 3.36 (m, 8H), 3.20 – 2.57 (m, 7H), 2.55 (s, 3H), 2.34 – 2.14 (m, 2H), 2.05 – 1.99 (m, 1H), 1.79 – 1.53 (m, 5H), 1.46 – 0.95 (m, 8H), 0.89 – 0.69 (m, 7H).
294		608.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.75 (m, 1H), 7.67 – 7.21 (m, 3H), 6.93 – 6.39 (m, 1H), 4.60 – 3.36 (m, 9H), 3.20 – 2.79 (m, 5H), 2.55 (s, 3H), 2.49 – 2.14 (m, 5H), 1.75 – 1.42 (m, 5H), 1.23 – 0.67 (m, 11H).
295		594.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.75 (m, 1H), 7.61 – 7.25 (m, 3H), 6.92 – 6.37 (m, 1H), 4.52 – 3.44 (m, 8H), 3.13 – 2.68 (m, 5H), 2.58 – 2.51 (m, 3H), 2.47 – 2.13 (m, 6H), 1.74 – 1.38 (m, 3H), 1.26 – 0.89 (m, 7H), 0.79 – 0.56 (m, 4H).
299		606.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.71 (m, 1H), 7.62 – 7.25 (m, 3H), 6.89 – 6.37 (m, 1H), 4.62 – 3.35 (m, 9H), 3.27 – 2.70 (m, 6H), 2.60 – 2.52 (m, 3H), 2.24 – 2.16 (m, 1H), 1.98 – 1.90 (m, 1H), 1.81 – 1.37 (m, 3H), 1.29 – 0.41 (m, 13H).
300		616.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.75 (m, 1H), 7.64 – 7.25 (m, 3H), 6.96 – 6.40 (m, 2H), 4.42 – 3.44 (m, 8H), 3.30 – 2.52 (m, 11H), 2.29 – 2.14 (m, 1H), 1.84 – 1.48 (m, 3H), 1.31 – 0.96 (m, 4H), 0.80 – 0.52 (m, 4H).
301		624.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.71 (m, 1H), 7.67 – 7.05 (m, 3H), 6.99 – 6.39 (m, 1H), 4.92 – 4.61 (m, 1H), 4.48 – 3.37 (m, 8H), 3.31 – 2.52 (m, 11H), 2.43 – 2.17 (m, 2H), 1.70 – 0.52 (m, 13H).
302		630.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.73 (m, 1H), 7.64 – 7.22 (m, 3H), 6.94 – 6.35 (m, 1H), 4.46 – 3.44 (m, 8H), 3.30 – 2.52 (m, 11H), 2.26 – 2.14 (m, 1H), 1.85 – 1.50 (m, 6H), 1.28 – 0.94 (m, 4H), 0.79 – 0.52 (m, 4H).
303		624.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.79 (m, 1H), 7.67 – 7.21 (m, 3H), 6.94 – 6.38 (m, 1H), 5.01 – 4.76 (m, 1H), 4.49 – 3.46 (m, 8H), 3.23 – 2.66 (m, 6H), 2.55 (s, 3H), 2.46 – 2.03 (m, 3H), 1.83 – 0.89 (m, 10H), 0.81 – 0.52 (m, 4H).

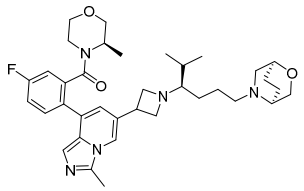
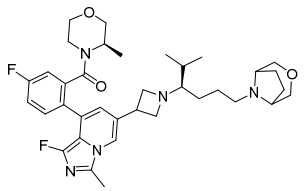
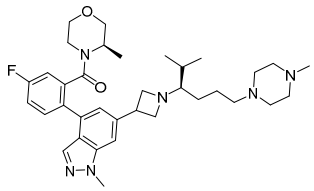
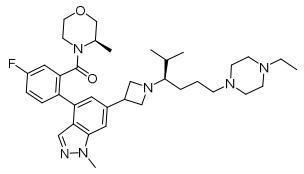
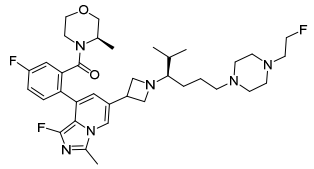
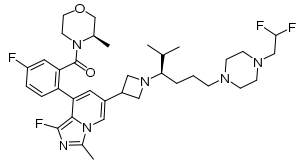
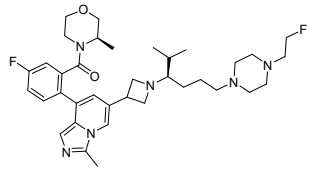
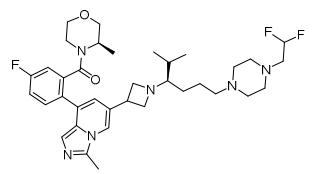
304		630.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.77 (m, 1H), 7.68 – 7.23 (m, 3H), 6.89 – 6.44 (m, 1H), 6.44 – 6.08 (m, 1H), 4.54 – 3.36 (m, 9H), 3.23 – 2.63 (m, 8H), 2.55 (s, 3H), 2.46 – 2.31 (m, 1H), 2.21 (s, 1H), 1.75 – 1.40 (m, 3H), 1.28 – 0.90 (m, 4H), 0.80 – 0.52 (m, 4H).
305		638.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.70 (m, 1H), 7.64 – 7.24 (m, 3H), 6.87 – 6.45 (m, 1H), 4.41 – 3.36 (m, 7H), 3.22 (s,3H), 3.18 – 2.59 (m, 7H), 2.55 (s, 3H), 2.47 – 2.17 (m, 3H), 2.08 – 1.99 (m, 1H), 1.92 – 1.77 (m, 2H), 1.76 – 1.65 (m, 2H), 1.64- 1.51 (m, 1H), 1.50 – 0.96 (m, 8H), 0.89 – 0.55 (m, 7H).
306		638.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 10.4 Hz, 1H), 7.64 – 7.20 (m, 3H), 6.81 – 6.35 (m, 1H), 4.48 – 3.38 (m, 7H), 3.23 – 2.83 (m, 9H), 2.67 – 2.53 (m, 4H), 2.39 – 2.20 (m, 2H), 2.08 – 1.98 (m, 1H), 1.92 – 1.78 (m, 2H), 1.78 – 1.66 (m, 2H), 1.64 – 1.54 (m, 1H), 1.52 – 0.92 (m, 9H), 0.83 (dd, J = 6.8, 12.4 Hz, 7H).
312-1		609.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 – 7.75 (m, 1H), 7.62 – 7.50 (m, 1H), 7.32 (dt, J = 2.4, 8.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 6.83 – 6.71 (m, 1H), 4.73 – 4.23 (m, 1H), 3.83 – 3.56 (m, 4H), 3.55 – 3.41 (m, 1H), 3.32 – 3.20 (m, 2H), 3.12 – 3.00 (m, 1H), 2.67 – 2.43 (m, 8H), 2.43 – 2.34 (m, 3H), 2.32 – 2.24 (m, 4H), 1.95 – 1.81 (m, 1H), 1.70 – 1.52 (m, 2H), 1.49 – 1.37 (m, 1H), 1.36 – 1.23 (m, 1H), 1.22 – 0.69 (m, 14H), 0.45 (d, J = 4.8 Hz, 2H).
312-2		609.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 – 7.79 (m, 1H), 7.57 – 7.47 (m, 1H), 7.40 – 7.24 (m, 2H), 6.77 – 6.54 (m, 1H), 3.56 – 3.40 (m, 4H), 3.18 – 2.87 (m, 4H), 2.56 – 2.52 (m, 3H), 2.40 – 2.14 (m, 10H), 2.13 – 2.09 (m, 3H), 2.03 – 1.99 (m, 1H), 1.75 – 1.64 (m, 1H), 1.49 – 1.36 (m, 2H), 1.31 – 1.07 (m, 3H), 0.99 – 0.89 (m, 3H), 0.86 – 0.78 (m, 9H), 0.46 – 0.32 (m, 2H).
313		637.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.81 – 7.73 (m, 1H), 7.60 – 7.48 (m, 1H), 7.30 (dt, J = 2.8, 8.4 Hz, 1H), 7.26 – 7.16 (m, 1H), 6.80 – 6.69 (m, 1H), 4.64 – 4.23 (m, 1H), 3.81 – 3.68 (m, 2H), 3.66 – 3.40 (m, 7H), 3.30 – 3.21 (m, 2H), 3.12 – 2.94 (m, 1H), 2.61 – 2.54 (m, 3H), 2.54 – 2.34 (m, 6H), 2.31 – 2.22 (m, 1H), 2.11 – 2.04 (m, 3H), 1.93 – 1.79 (m, 1H), 1.69 – 1.52 (m, 2H), 1.48 – 1.37 (m, 1H), 1.36 – 1.24 (m, 1H), 1.01 – 0.82 (m, 12H), 0.42 (d, J = 5.6 Hz, 2H).
314		626.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.79 (m, 1H), 7.61 – 7.47 (m, 1H), 7.44 – 7.24 (m, 2H), 6.84 – 6.43 (m, 1H), 4.74 – 4.51 (m, 1H), 4.44 – 3.37 (m, 7H), 3.16 – 2.77 (m, 4H), 2.57 – 2.52 (m, 3H), 2.48 – 2.41 (m, 2H), 2.26 – 2.16 (m, 4H), 2.07 – 2.00 (m, 1H), 1.85 – 1.59 (m, 5H), 1.51 – 1.36 (m, 2H), 1.30 – 1.05 (m, 4H), 0.98 – 0.38 (m, 8H).
315		526.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.87 – 7.80 (m, 1H), 7.61 – 7.50 (m, 1H), 7.30 (dt, J = 2.4, 8.4 Hz, 1H), 7.25 – 7.15 (m, 1H), 6.74 – 6.64 (m, 1H), 4.75 – 4.59 (m, 1H), 4.50 – 4.26 (m, 2H), 4.21 – 4.02 (m, 1H), 4.00 – 3.87 (m, 1H), 3.65 – 3.53 (m, 1H), 3.50 – 3.37 (m, 1H), 3.16 – 3.01 (m, 1H), 3.00 – 2.87 (m, 1H), 2.59 (s, 3H), 2.37 – 2.25 (m, 3H), 1.98 – 1.78 (m, 1H), 1.11 – 0.82 (m, 13H), 0.45 (d, J = 4.8

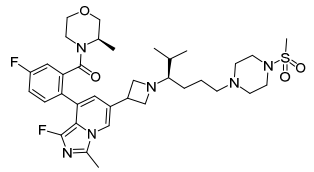
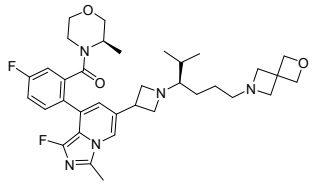
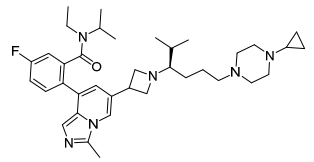
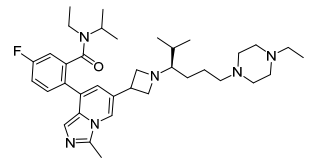
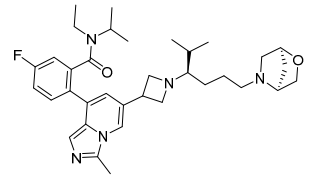
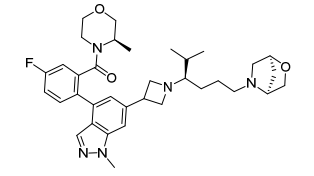
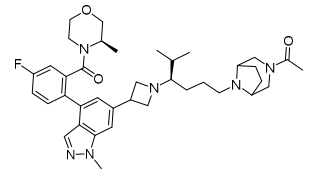
			Hz, 2H).
316		540.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.79 (m, 1H), 7.61 – 7.50 (m, 1H), 7.30 (dt, J = 2.0, 8.4 Hz, 1H), 7.25 – 7.13 (m, 1H), 6.74 – 6.61 (m, 1H), 4.74 – 4.62 (m, 1H), 4.48 – 4.25 (m, 2H), 4.21 – 4.02 (m, 1H), 3.99 – 3.87 (m, 1H), 3.65 – 3.54 (m, 1H), 3.50 – 3.38 (m, 1H), 3.12 – 2.95 (m, 2H), 2.59 (s, 3H), 2.36 – 2.25 (m, 3H), 1.74 – 1.55 (m, 2H), 1.25 – 1.12 (m, 1H), 1.07 – 0.82 (m, 13H), 0.51 – 0.37 (m, 2H).
317		552.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.80 (m, 1H), 7.64 – 7.49 (m, 1H), 7.36 – 7.26 (m, 1H), 7.24 – 7.14 (m, 1H), 6.74 – 6.60 (m, 1H), 4.75 – 4.63 (m, 1H), 4.51 – 4.26 (m, 2H), 4.22 – 4.02 (m, 1H), 3.99 – 3.81 (m, 1H), 3.65 – 3.54 (m, 1H), 3.49 – 3.38 (m, 1H), 3.12 – 2.97 (m, 2H), 2.59 (s, 3H), 2.37 – 2.27 (m, 3H), 2.11 – 1.97 (m, 1H), 1.94 – 1.80 (m, 1H), 1.76 – 1.48 (m, 5H), 1.44 – 1.23 (m, 2H), 1.16 – 0.82 (m, 7H), 0.55 – 0.39 (m, 2H).
318		540.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.67 – 7.57 (m, 1H), 7.42 – 7.28 (m, 1H), 7.09 (t, J = 8.4 Hz, 1H), 7.03 – 6.94 (m, 1H), 6.59 – 6.43 (m, 1H), 4.50 (t, J = 9.0 Hz, 1H), 4.45 – 4.35 (m, 1H), 4.31 – 4.13 (m, 2H), 4.12 – 4.01 (m, 1H), 4.00 – 3.81 (m, 1H), 3.79 – 3.65 (m, 1H), 3.44 – 3.32 (m, 1H), 3.29 – 3.16 (m, 1H), 2.94 – 2.77 (m, 2H), 2.39 (s, 3H), 2.13 – 2.04 (m, 3H), 1.53 – 1.37 (m, 1H), 1.36 – 1.23 (m, 1H), 1.13 – 0.94 (m, 1H), 0.80 (d, J = 6.0 Hz, 2H), 0.76 – 0.64 (m, 9H), 0.25 (d, J = 4.8 Hz, 2H).
320		590.4	^{1}H NMR (400 MHz,CD_3OD) δ 8.00 – 7.87 (m, 1H), 7.85 – 7.63 (m, 1H), 7.46 – 7.04 (m, 3H), 7.03 – 6.70 (m, 1H), 4.67 – 4.30 (m, 2H), 4.08 – 3.65 (m, 5H), 3.61 – 3.50 (m, 1H), 3.27 – 2.92 (m, 5H), 2.83 – 2.48 (m, 5H), 2.42 – 2.33 (m, 3H), 1.98 – 1.67 (m, 3H), 1.67 – 1.54 (m, 3H), 1.34 – 1.09 (m, 4H), 1.00 – 0.93 (m, 3H), 0.91 – 0.84 (m, 3H), 0.75 – 0.40 (m, 1H).
324-1		619.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.78 – 7.60 (m, 1H), 7.47 – 7.27 (m, 2H), 7.13 – 6.96 (m, 1H), 6.92 – 6.68 (m, 1H), 4.38 – 3.84 (m, 1H), 3.72 – 3.41 (m, 5H), 3.25 – 3.03 (m, 4H), 3.01 – 2.91 (m, 1H), 2.87 – 2.69 (m, 1H), 2.62 – 2.57 (m, 3H), 2.38 – 2.17 (m, 11H), 2.07 – 2.00 (m, 1H), 1.92 – 1.63 (m, 2H), 1.49 – 1.38 (m, 2H), 1.28 – 1.12 (m, 3H), 1.06 – 1.00 (m, 1H), 0.99 – 0.92 (m, 3H), 0.88 – 0.80 (m, 6H), 0.69 – 0.40 (m, 1H).
324-2		619.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 7.85 (m, 1H), 7.83 – 7.57 (m, 1H), 7.48 – 7.24 (m, 2H), 7.15 – 6.58 (m, 2H), 4.39 – 3.37 (m, 6H), 3.29 – 2.53 (m, 9H), 2.43 – 1.99 (m, 12H), 1.91 – 1.09 (m, 7H), 1.08 – 0.77 (m, 10H), 0.72 – 0.37 (m, 1H).
325		631.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.90 (m, 1H), 7.78 – 7.59 (m, 1H), 7.47 – 7.27 (m, 2H), 7.10 – 6.90 (m, 1H), 6.89 – 6.59 (m, 1H), 4.37 – 3.83 (m, 1H), 3.78 – 3.40 (m, 5H), 3.25 – 2.65 (m, 6H), 2.62 – 2.57 (m, 3H), 2.48 – 2.40 (m, 3H), 2.37 – 2.14 (m, 6H), 2.08 – 2.01 (m, 1H), 1.94 – 1.60 (m, 2H), 1.56 – 1.37 (m, 3H), 1.27 – 1.12 (m, 3H), 1.07 – 0.98 (m, 1H), 0.89 – 0.77 (m, 6H), 0.72 – 0.58 (m, 1H), 0.40 – 0.33 (m, 2H), 0.27 – 0.20 (m, 2H).

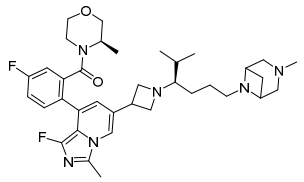
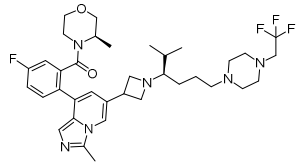
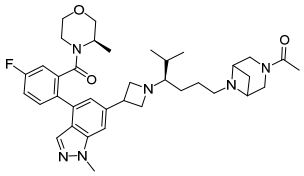
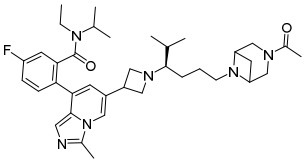
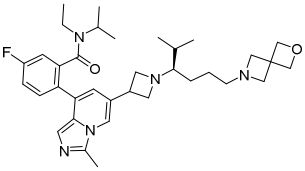
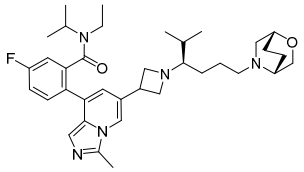
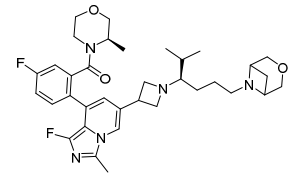
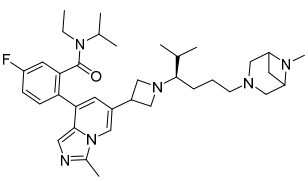
326		592.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.85 (m, 1H), 7.76 – 7.59 (m, 1H), 7.46 – 7.21 (m, 2H), 7.12 – 6.95 (m, 1H), 6.88 – 6.66 (m, 1H), 4.55 – 4.23 (m, 1H), 3.76 – 3.35 (m, 5H), 3.29 – 2.62 (m, 6H), 2.61 – 2.57 (m, 3H), 2.34 – 2.16 (m, 2H), 2.06 – 1.99 (m, 1H), 1.80 – 1.52 (m, 5H), 1.50 – 1.31 (m, 3H), 1.27 – 0.72 (m, 16H), 0.31 – 0.25 (m, 2H).
327		592.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.86 (m, 1H), 7.74 – 7.61 (m, 1H), 7.44 – 7.24 (m, 2H), 7.13 – 6.92 (m, 1H), 6.89 – 6.65 (m, 1H), 4.56 – 4.22 (m, 1H), 3.60 – 3.36 (m, 5H), 3.25 – 2.61 (m, 6H), 2.60 – 2.57 (m, 3H), 2.33 – 2.14 (m, 2H), 2.06 – 1.97 (m, 1H), 1.79 – 1.53 (m, 5H), 1.48 – 1.30 (m, 3H), 1.27 – 0.96 (m, 4H), 0.92 – 0.71 (m, 12H), 0.31 – 0.25 (m, 2H).
328		665.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.45 (m, 2H), 7.27 – 7.01 (m, 2H), 6.93 – 6.69 (m, 1H), 5.13 – 4.77 (m, 4H), 4.60 – 4.27 (m, 3H), 4.19 – 3.99 (m, 2H), 3.97 – 3.67 (m, 3H), 3.66 – 3.06 (m, 6H), 3.02 – 2.68 (m, 5H), 2.61 (s, 3H), 2.53 – 2.31 (m, 2H), 2.15 – 1.97 (m, 4H), 1.57 – 1.23 (m, 2H), 1.19 – 0.86 (m, 10H), 0.78 – 0.57 (m, 1H).
329		665.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.75 (m, 1H), 7.63 – 7.23 (m, 3H), 6.85 – 6.38 (m, 1H), 4.40 – 3.44 (m, 8H), 3.25 – 2.52 (m, 12H), 2.45 – 1.79 (m, 8H), 1.77 – 1.63 (m, 1H), 1.48 – 1.35 (m, 2H), 1.28 – 0.98 (m, 4H), 0.96 – 0.68 (m, 10H).
331		665.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.75 (m, 1H), 7.64 – 7.23 (m, 3H), 6.85 – 6.40 (m, 1H), 4.52 – 3.44 (m, 8H), 3.25 – 2.52 (m, 11H), 2.29 – 1.63 (m, 10H), 1.52 – 1.02 (m, 9H), 0.90 – 0.69 (m, 7H).
333		663.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 14.0 Hz, 1H), 7.66 – 7.50 (m, 1H), 7.42 – 7.14 (m, 2H), 6.92 – 6.54 (m, 1H), 4.67 – 4.35 (m, 2H), 4.08 (d, J = 12.4 Hz, 1H), 3.84 – 3.53 (m, 7H), 3.38 (d, J = 10.0 Hz, 1H), 3.28 – 3.08 (m, 3H), 3.04 – 2.82 (m, 2H), 2.69 – 2.50 (m, 6H), 2.32 – 2.21 (m, 1H), 2.08 (s, 2H), 2.00 – 1.69 (m, 5H), 1.63 – 1.50 (m, 2H), 1.48 – 1.38 (m, 1H), 1.36 – 1.26 (m, 2H), 1.22 – 1.09 (m, 1H), 0.93 (dd, J = 6.4, 17.2 Hz, 6H), 0.85 – 0.75 (m, 1H).
334		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.75 (m, 1H), 7.65 – 7.19 (m, 3H), 6.88 – 6.34 (m, 1H), 4.39 – 3.35 (m, 9H), 3.24 – 2.90 (m, 6H), 2.85 – 2.52 (m, 8H), 2.04 – 1.88 (m, 4H), 1.76 – 1.62 (m, 1H), 1.42 – 1.29 (m, 2H), 1.27 – 1.03 (m, 4H), 0.88 – 0.70 (m, 7H), 0.55 – 0.37 (m, 4H).
335		665.4	^{1}H NMR (400 MHz, DMSO-d_6) δ (400 MHz, DMSO-d6) δ = 7.96 – 7.76 (m, 1H), 7.63 – 7.22 (m, 3H), 6.85 – 6.42 (m, 1H), 4.45 – 3.33 (m, 11H), 3.26 – 2.70 (m, 5H), 2.55 (s, 3H), 2.35 – 2.18 (m, 8H), 2.04 (d, J = 2.4 Hz, 1H), 1.78 – 1.63 (m, 1H), 1.52 – 1.38 (m, 2H), 1.32 – 1.02 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.89 – 0.58 (m, 7H).

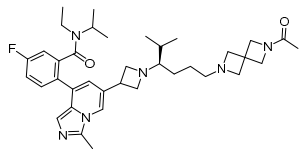
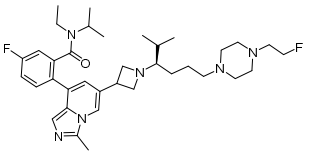
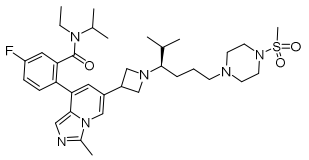
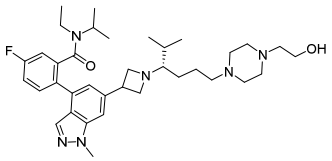
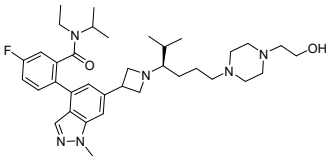
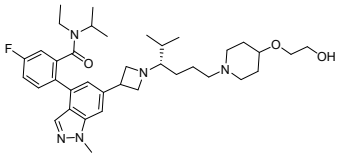
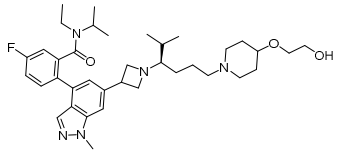
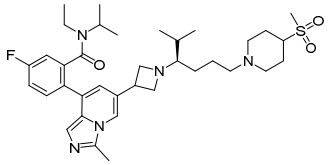
336		679.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.79 (m, 1H), 7.63 – 7.23 (m, 3H), 6.80 – 6.46 (m, 1H), 4.36 – 3.34 (m, 9H), 3.21 – 2.63 (m, 7H), 2.54 (s, 3H), 2.44 (m, 1H), 2.40 – 2.31 (m, 1H), 2.27 – 2.18 (m, 2H), 2.06 – 1.90 (m, 4H), 1.77 – 1.65 (m, 1H), 1.37 (s, 2H), 1.29 – 1.04 (m, 4H), 0.92 (s, 3H), 0.90 – 0.72 (m, 10H).
337		677.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.34 (m, 2H), 7.25 – 7.05 (m, 2H), 6.82 – 6.56 (m, 1H), 4.66 – 4.06 (m, 2H), 3.82 – 3.29 (m, 7H), 3.25 – 2.54 (m, 10H), 2.30 (br t, J = 6.9 Hz, 2H), 2.09 (br s, 1H), 2.05 (s, 3H), 1.95 – 1.76 (m, 3H), 1.70 (br s, 3H), 1.62 – 1.45 (m, 4H), 1.43 – 1.04 (m, 4H), 0.94 – 0.87 (m, 5H), 0.83 – 0.57 (m, 1H).
338		679.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 14.0 Hz, 1H), 7.64 – 7.51 (m, 1H), 7.38 – 7.17 (m, 2H), 6.86 – 6.59 (m, 1H), 4.79 – 3.97 (m, 2H), 3.77 (t, J = 6.0 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.67 – 3.43 (m, 7H), 3.28 – 3.21 (m, 2H), 3.19 – 3.06 (m, 1H), 3.04 – 2.86 (m, 2H), 2.60 (s, 3H), 2.52 – 2.34 (m, 6H), 2.33 – 1.95 (m, 2H), 1.92 – 1.78 (m, 1H), 1.69 – 1.51 (m, 2H), 1.48 – 1.37 (m, 1H), 1.30 (d, J = 5.2 Hz, 2H), 1.17 (d, J = 4.8 Hz, 1H), 1.08 (d, J = 6.6 Hz, 6H), 0.94 (dd, J = 6.2, 16.8 Hz, 6H), 0.81 (d, J = 5.2 Hz, 1H).
339		679.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.78 (m, 1H), 7.61 – 7.24 (m, 3H), 6.78 – 6.45 (m, 1H), 4.39 – 3.38 (m, 7H), 3.19 – 2.65 (m, 5H), 2.57 – 2.53 (m, 3H), 2.39 – 2.30 (m, 2H), 2.26 – 2.16 (m, 2H), 2.12 – 2.01 (m, 3H), 1.93 (s, 3H), 1.78 – 1.64 (m, 1H), 1.51 – 1.04 (m, 13H), 0.97 – 0.50 (m, 8H).
340		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.75 (m, 1H), 7.66 – 7.23 (m, 3H), 6.85 – 6.39 (m, 1H), 4.40 – 3.37 (m, 8H), 3.15 – 2.53 (m, 9H), 2.41 – 1.88 (m, 10H), 1.75 – 1.65 (m, 1H), 1.48 – 1.01 (m, 7H), 0.89 – 0.52 (m, 10H).
341		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.77 (m, 1H), 7.63 – 7.21 (m, 3H), 6.82 – 6.42 (m, 1H), 4.42 – 3.35 (m, 11H), 3.15 – 2.65 (m, 4H), 2.55 (s, 3H), 2.40 – 2.19 (m, 6H), 2.10 – 2.00 (m, 1H), 1.98 – 1.86 (m, 1H), 1.78 – 1.65 (m, 1H), 1.53 – 1.38 (m, 2H), 1.32 – 1.03 (m, 4H), 0.98 – 0.49 (m, 12H).
342		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.71 (m, 1H), 7.70 – 7.16 (m, 3H), 7.01 – 6.16 (m, 1H), 4.39 – 4.17 (m, 1H), 4.00 – 3.65 (m, 2H), 3.62 – 3.42 (m, 6H), 3.20 – 2.63 (m, 9H), 2.58 – 2.52 (m, 3H), 2.48 – 2.32 (m, 3H), 2.07 – 1.99 (m, 1H), 1.95 – 1.85 (m, 3H), 1.80 – 1.58 (m, 3H), 1.57 – 1.32 (m, 3H), 1.31 – 1.02 (m, 4H), 0.98 – 0.58 (m, 7H).
343		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.76 (m, 1H), 7.64 – 7.23 (m, 3H), 6.87 – 6.44 (m, 1H), 4.43 – 4.16 (m, 1H), 4.09 – 3.62 (m, 2H), 3.60 – 3.36 (m, 6H), 3.20 – 2.63 (m, 9H), 2.61 – 2.52 (m, 3H), 2.49 – 2.37 (m, 3H), 2.09 – 1.98 (m, 1H), 1.94 – 1.88 (m, 3H), 1.79 – 1.60 (m, 3H), 1.56 – 1.34 (m, 3H), 1.31 – 1.05 (m, 4H), 0.89 – 0.69 (m, 7H).

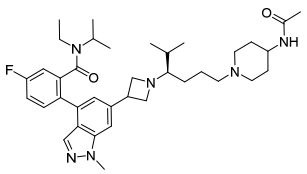
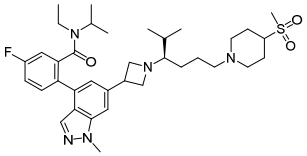
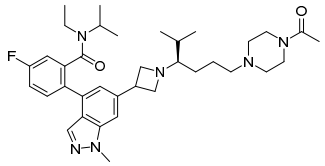
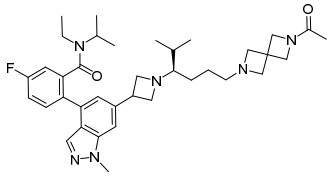
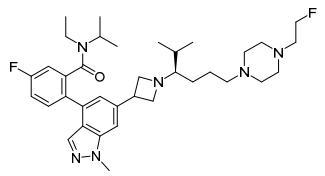
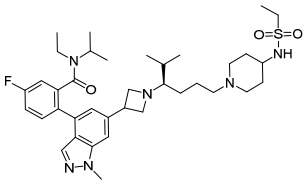
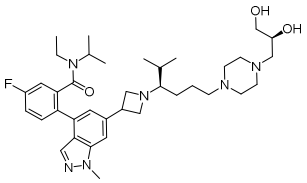
344		677.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.30 (m, 2H), 7.25 – 7.01 (m, 2H), 6.80 – 6.58 (m, 1H), 4.67 – 3.93 (m, 3H), 3.75 – 2.92 (m, 9H), 2.78 – 2.44 (m, 5H), 2.36 – 2.09 (m, 4H), 2.05 (s, 3H), 1.98 – 1.71 (m, 5H), 1.70 – 1.05 (m, 9H), 0.98 – 0.52 (m, 7H).
345		663.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.76 (m, 1H), 7.66 – 7.21 (m, 3H), 6.92 – 6.40 (m, 1H), 4.39 – 3.35 (m, 9H), 3.23 – 2.52 (m, 12H), 2.42 (t, J = 7.2 Hz, 2H), 2.30 (q, J = 6.4 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.79 – 1.65 (m, 5H), 1.53 – 1.37 (m, 2H), 1.31 – 1.02 (m, 4H), 0.89 – 0.67 (m, 7H).
346		663.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.75 (m, 1H), 7.63 – 7.20 (m, 3H), 6.82 – 6.43 (m, 1H), 4.37 – 3.36 (m, 11H), 3.29 – 2.64 (m, 7H), 2.54 (s, 3H), 2.38 – 2.20 (m, 3H), 2.06 – 1.91 (m, 4H), 1.76 – 1.63 (m, 1H), 1.41 – 1.03 (m, 7H), 0.89 – 0.54 (m, 7H).
347		645.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.88 (m, 1H), 7.81 – 7.59 (m, 1H), 7.48 – 7.26 (m, 2H), 7.12 – 6.91 (m, 1H), 6.88 – 6.62 (m, 1H), 4.49 – 3.34 (m, 9H), 3.30 – 2.65 (m, 8H), 2.60 (s, 3H), 2.48 – 2.30 (m, 3H), 2.08 – 2.00 (m, 1H), 1.93 (s, 1H), 1.89 – 1.80 (m, 2H), 1.78 – 1.50 (m, 3H), 1.46 – 1.13 (m, 5H), 1.03 (d, J = 6.8 Hz, 1H), 0.84 (dd, J = 7.2, 12.0 Hz, 6H), 0.70 – 0.37 (m, 1H).
349		635.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.29 (m, 2H), 7.26 – 6.97 (m, 2H), 6.93 – 6.61 (m, 1H), 4.64 – 4.04 (m, 6H), 4.00 – 3.48 (m, 12H), 3.36 – 3.05 (m, 5H), 2.99 – 2.85 (m, 2H), 2.77 – 2.64 (m, 3H), 2.61 (s, 3H), 2.47 – 1.94 (m, 3H), 1.77 – 1.57 (m, 2H), 1.31 – 1.15 (m, 1H), 1.05 – 0.92 (m, 5H), 0.81 – 0.56 (m, 1H).
350		649.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.78 (m, 1H), 7.61 – 7.23 (m, 3H), 6.85 – 6.42 (m, 1H), 4.43 – 3.34 (m, 7H), 3.23 – 2.64 (m, 5H), 2.57 – 2.52 (m, 3H), 2.49 – 2.42 (m, 4H), 2.36 – 2.10 (m, 6H), 2.07 – 1.98 (m, 1H), 1.75 – 1.63 (m, 1H), 1.58 – 1.34 (m, 3H), 1.31 – 1.03 (m, 4H), 0.89 – 0.72 (m, 7H), 0.40 – 0.32 (m, 2H), 0.28 – 0.19 (m, 2H).
352		622.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.75 (m, 1H), 7.63 – 7.24 (m, 3H), 6.83 – 6.40 (m, 1H), 4.40 – 3.35 (m, 11H), 3.24 – 2.52 (m, 9H), 2.49 – 2.29 (m, 3H), 2.06 – 1.99 (m, 1H), 1.76 – 1.64 (m, 2H), 1.56 – 1.47 (m, 1H), 1.44 – 1.33 (m, 2H), 1.32 – 1.05 (m, 4H), 0.90 – 0.69 (m, 7H).
354		618.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.00 – 7.89 (m, 1H), 7.85 – 7.63 (m, 1H), 7.42 – 7.21 (m, 2H), 7.21 – 7.08 (m, 1H), 7.05 – 6.76 (m, 1H), 4.51 – 4.01 (m, 2H), 3.84 – 3.76 (m, 2H), 3.75 – 3.66 (m, 3H), 3.62 – 3.51 (m, 1H), 3.34 – 3.29 (m, 4H), 3.28 – 3.16 (m, 2H), 3.14 – 2.96 (m, 2H), 2.94 – 2.86 (m, 1H), 2.75 – 2.65 (m, 4H), 2.64 – 2.55 (m, 2H), 2.34 – 2.23 (m, 1H), 2.12 – 1.96 (m, 2H), 1.91 – 1.82 (m, 1H), 1.79 – 1.67 (m, 2H), 1.64 – 1.52 (m, 2H), 1.49 – 1.40 (m, 1H), 1.39 – 1.31 (m, 1H), 1.27 (d, J = 7.2 Hz, 1H), 1.16 – 1.07 (m, 1H), 1.00 – 0.86 (m, 6H), 0.78 – 0.37 (m, 1H).

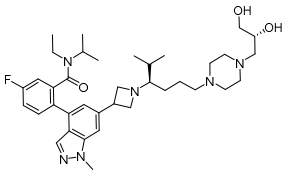
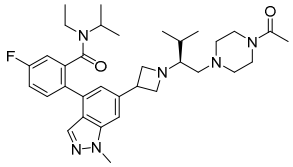
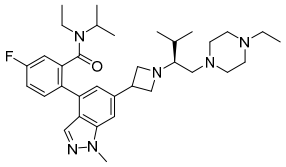
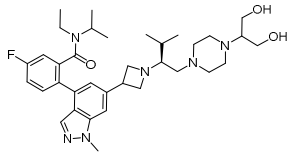
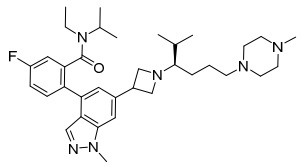
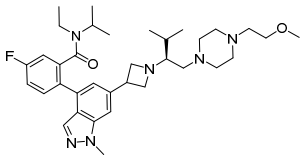
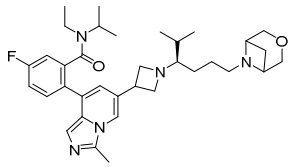
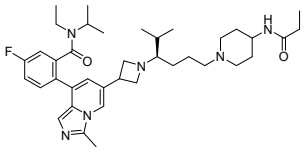
355		618.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.88 (m, 1H), 7.80 – 7.59 (m, 1H), 7.51 – 7.27 (m, 2H), 7.13 – 6.91 (m, 1H), 6.89 – 6.62 (m, 1H), 4.41 – 3.38 (m, 9H), 3.28 – 3.05 (m, 3H), 3.02 – 2.90 (m, 1H), 2.88 – 2.66 (m, 3H), 2.60 (s, 3H), 2.54 (s, 1H), 2.48 – 2.42 (m, J = 7.0, 7.0 Hz, 2H), 2.12 – 0.97 (m, 13H), 0.93 – 0.76 (m, 6H), 0.69 – 0.38 (m, 1H).
356		636.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 13.6 Hz, 1H), 7.66 – 7.49 (m, 1H), 7.40 – 7.12 (m, 2H), 6.88 – 6.59 (m, 1H), 4.64 – 3.98 (m, 1H), 3.85 – 3.53 (m, 7H), 3.48 (d, J = 9.2 Hz, 2H), 3.35 – 3.20 (m, 4H), 3.11 (s, 2H), 3.07 – 2.65 (m, 2H), 2.60 (s, 3H), 2.37 – 2.20 (m, 3H), 2.03 – 1.76 (m, 5H), 1.57 (s, 2H), 1.48 – 1.36 (m, 1H), 1.35 – 1.23 (m, 2H), 1.17 (d, J = 4.8 Hz, 1H), 0.94 (dd, J = 6.4, 17.6 Hz, 6H), 0.85 – 0.59 (m, 1H).
358		605.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.02 – 7.85 (m, 1H), 7.78 – 7.54 (m, 2H), 7.46 – 7.12 (m, 3H), 4.57 – 4.37 (m, 2H), 4.29 – 4.21 (m, 2H), 4.17 – 4.03 (m, 4H), 3.70 – 3.39 (m, 2H), 3.27 – 3.14 (m, 2H), 3.08 – 2.90 (m, 5H), 2.82 – 2.68 (m, 3H), 2.65 (d, J = 6.4 Hz, 3H), 2.62 – 2.54 (m, 2H), 2.50 – 2.23 (m, 1H), 2.21 – 2.08 (m, 1H), 2.04 (s, 2H), 1.75 – 1.63 (m, 3H), 1.58 – 1.20 (m, 3H), 1.12 – 0.99 (m, 7H), 0.47 (d, J = 6.8 Hz, 1H).
359		619.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.96 – 7.83 (m, 1H), 7.75 – 7.50 (m, 2H), 7.44 – 7.05 (m, 3H), 4.58 (s, 3H), 4.15 – 4.07 (m, 3H), 3.96 – 3.86 (m, 3H), 3.66 – 3.41 (m, 2H), 2.56 – 2.31 (m, 10H), 2.19 (s, 1H), 2.10 – 1.99 (m, 1H), 1.96 – 1.84 (m, 1H), 1.73 – 1.53 (m, 3H), 1.52 – 1.36 (m, 2H), 1.33 (s, 1H), 1.29 (s, 2H), 1.23 (d, J = 7.0 Hz, 1H), 1.12 – 1.05 (m, 4H), 0.99 – 0.88 (m, 7H), 0.51 (d, J = 6.9 Hz, 1H).
361		655.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.70 (m, 1H), 7.63 – 7.47 (m, 1H), 7.45 – 7.22 (m, 2H), 6.94 – 6.31 (m, 1H), 4.59 – 4.39 (m, 2H), 4.38 – 3.34 (m, 7H), 3.28 – 2.57 (m, 7H), 2.57 – 2.53 (m, 3H), 2.46 – 2.16 (m, 10H), 2.07 – 1.99 (m, 1H), 1.77 – 1.62 (m, 1H), 1.52 – 1.34 (m, 2H), 1.32 – 1.02 (m, 4H), 0.91 – 0.65 (m, 7H).
362		673.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.74 (m, 1H), 7.65 – 7.17 (m, 3H), 6.88 – 6.44 (m, 1H), 6.35 – 5.88 (m, 1H), 4.45 – 3.32 (m, 7H), 3.23 – 2.59 (m, 7H), 2.55 (s, 3H), 2.48 – 2.16 (m, 10H), 2.08 – 1.96 (m, 1H), 1.78 – 1.60 (m, 1H), 1.51 – 1.33 (m, 2H), 1.31 – 1.02 (m, 4H), 0.89 – 0.62 (m, 7H).
363		637.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.51 (m, 2H), 7.25 – 7.13 (m, 3H), 6.92 – 6.70 (m, 1H), 4.79 – 4.50 (m, 3H), 3.80 – 3.47 (m, 5H), 3.42 – 2.86 (m, 6H), 2.76 – 2.71 (m, 1H), 2.70 (s, 3H), 2.68 – 2.65 (m, 1H), 2.62 – 2.47 (m, 6H), 2.35 – 2.29 (m, 2H), 2.15 – 2.04 (m, 1H), 1.90 – 1.75 (m, 2H), 1.59 – 1.49 (m, 3H), 1.35 – 1.23 (m, 3H), 1.14 – 1.08 (m, 1H), 0.95 – 0.88 (m, 6H), 0.81 – 0.76 (m, 1H).
364		655.8	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 – 7.87 (m, 1H), 7.85 – 7.64 (m, 1H), 7.42 – 7.22 (m, 2H), 7.21 – 7.06 (m, 1H), 7.03 – 6.77 (m, 1H), 6.13 – 5.77 (m, 1H), 4.57 – 4.00 (m, 1H), 3.86 – 3.33 (m, 6H), 3.29 – 3.22 (m, 2H), 3.22 – 2.91 (m, 2H), 2.85 – 2.72 (m, 2H), 2.71 – 2.65 (m, 4H), 2.63 (s, 3H), 2.52 (s, 4H), 2.40 – 2.31 (m, 2H), 2.29 – 2.23 (m, 1H),

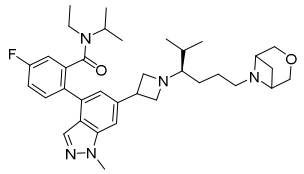
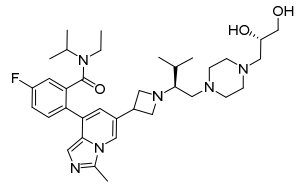
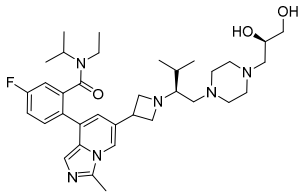
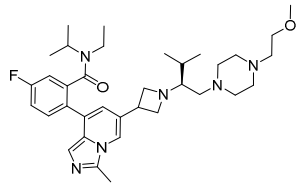
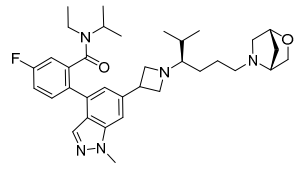
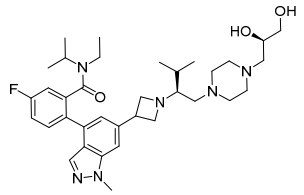
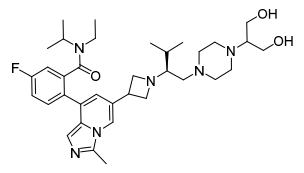
			2.01 – 1.76 (m, 2H), 1.66 – 1.52 (m, 2H), 1.47 – 1.35 (m, 1H), 1.34 – 1.24 (m, 2H), 1.12 (d, J = 6.8 Hz, 1H), 1.00 – 0.85 (m, 6H), 0.76 – 0.39 (m, 1H).
365		687.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.78 (m, 1H), 7.63 – 7.24 (m, 3H), 6.84 – 6.46 (m, 1H), 4.39 – 3.34 (m, 7H), 3.28 – 2.94 (m, 8H), 2.85 (s, 4H), 2.55 (s, 3H), 2.41 (s, 4H), 2.35 – 2.22 (m, 2H), 2.08 – 1.99 (m, 1H), 1.77 – 1.65 (m, 1H), 1.56 – 1.34 (m, 2H), 1.32 – 1.03 (m, 4H), 0.96 – 0.73 (m, 7H).
369		622.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.71 (m, 1H), 7.63 – 7.47 (m, 1H), 7.45 – 7.24 (m, 2H), 6.84 – 6.40 (m, 1H), 4.76 – 4.46 (m, 4H), 4.42 – 3.36 (m, 7H), 3.20 – 2.70 (m, 9H), 2.59 – 2.52 (m, 3H), 2.27 – 2.17 (m, 2H), 2.03 – 1.93 (m, 1H), 1.75 – 1.61 (m, 1H), 1.32 – 1.02 (m, 6H), 0.88 – 0.65 (m, 7H).
376		617.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 – 7.64 (m, 1H), 7.50 – 7.37 (m, 1H), 7.21 – 7.01 (m, 2H), 6.90 – 6.72 (m, 1H), 6.61 – 6.44 (m, 1H), 4.11 – 3.09 (m, 5H), 3.04 – 2.41 (m, 5H), 2.37 – 2.32 (m, 3H), 2.11 – 1.90 (m, 6H), 1.83 – 1.73 (m, 1H), 1.53 – 1.41 (m, 1H), 1.33 – 1.13 (m, 3H), 1.06 – 0.78 (m, 3H), 0.70 – 0.46 (m, 13H), 0.20 - -0.10 (m, 7H).
377		605.6	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.83 (m, 1H), 7.77 – 7.66 (m, 1H), 7.38 – 7.04 (m, 3H), 6.97 – 6.84 (m, 1H), 4.40 – 3.36 (m, 6H), 3.29 – 3.22 (m, 1H), 3.10 – 2.94 (m, 1H), 2.74 – 2.33 (m, 14H), 2.30 – 2.21 (m, 1H), 1.92 – 1.81 (m, 1H), 1.69 – 1.04 (m, 9H), 1.01 – 0.76 (m, 12H), 0.30 (d, J = 6.4 Hz, 2H).
380		590.8	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.89 (m, 1H), 7.76 – 7.68 (m, 1H), 7.34 (dt, J = 2.4, 8.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.17 – 7.12 (m, 1H), 6.95 – 6.86 (m, 1H), 4.44 – 4.27 (m, 1H), 4.06 – 3.97 (m, 1H), 3.82 – 3.75 (m, 1H), 3.74 – 3.63 (m, 2H), 3.63 – 3.52 (m, 3H), 3.50 – 3.38 (m, 1H), 3.28 – 3.21 (m, 1H), 3.03 (td, J = 6.4, 12.4 Hz, 1H), 2.89 – 2.81 (m, 1H), 2.66 (s, 3H), 2.64 – 2.49 (m, 3H), 2.30 – 2.22 (m, 1H), 1.93 – 1.81 (m, 2H), 1.78 – 1.68 (m, 1H), 1.66 – 1.50 (m, 2H), 1.49 – 1.38 (m, 1H), 1.37 – 1.25 (m, 1H), 1.19 – 1.09 (m, 1H), 1.00 – 0.87 (m, 12H), 0.80 (t, J = 7.0 Hz, 1H), 0.30 (d, J = 6.8 Hz, 2H).
382		604.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.98 – 6.81 (m, 6H), 4.32 – 4.11 (m, 1H), 3.98 – 3.89 (m, 3H), 3.88 – 3.78 (m, 1H), 3.77 – 3.62 (m, 3H), 3.48 – 3.38 (m, 2H), 3.36 – 3.21 (m, 1H), 3.20 – 3.01 (m, 5H), 3.00 – 2.80 (m, 1H), 2.79 – 2.60 (m, 2H), 2.58 – 2.15 (m, 4H), 2.14 – 2.01 (m, 1H), 1.83 – 1.63 (m, 2H), 1.60 – 1.52 (m, 1H), 1.51 – 1.34 (m, 2H), 1.34 – 1.22 (m, 1H), 1.21 – 1.11 (m, 1H), 1.06 (d, J = 7.2 Hz, 1H), 0.97 – 0.62 (m, 7H), 0.36 - -0.01 (m, 1H).
383		659.7	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 – 7.74 (m, 1H), 7.72 – 7.50 (m, 2H), 7.48 – 7.23 (m, 2H), 7.17 – 6.91 (m, 1H), 4.34 – 3.79 (m, 5H), 3.75 – 3.35 (m, 6H), 3.27 – 2.54 (m, 10H), 2.28 – 2.21 (m, 2H), 2.10 – 2.02 (m, 1H), 1.96 – 1.88 (m, 3H), 1.83 – 1.70 (m, 3H), 1.52 – 1.39 (m, 3H), 1.36 – 1.23 (m, 3H), 1.16 – 1.08 (m, 1H), 1.01 – 0.95 (m, 1H), 0.90 – 0.82 (m, 6H), 0.53 – 0.16 (m, 1H).

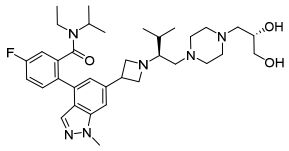
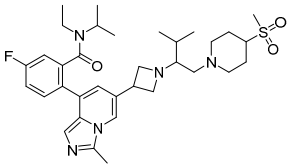
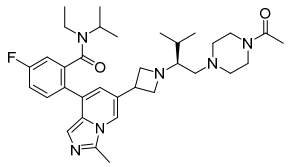
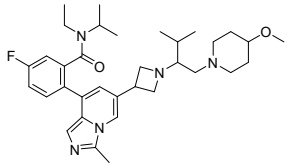
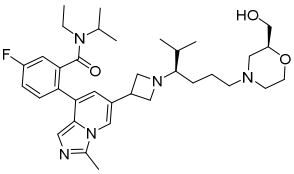
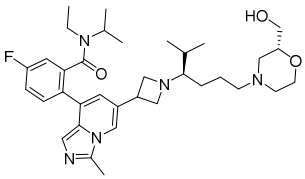
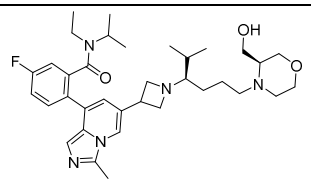
384		635.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.75 (m, 1H), 7.61 – 7.22 (m, 3H), 6.82 – 6.45 (m, 1H), 4.41 – 3.34 (m, 10H), 3.21 – 2.81 (m, 4H), 2.76 – 2.70 (m, 2H), 2.70 – 2.64 (m, 2H), 2.54 (s, 3H), 2.28 (s, 3H), 2.22 (s, 2H), 2.18 – 2.08 (m, 1H), 2.00 (s, 1H), 1.82 – 1.07 (m, 8H), 0.91 – 0.58 (m, 7H).
385		673.7	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.54 (m, 2H), 7.26 – 7.12 (m, 3H), 6.99 – 6.68 (m, 1H), 4.62 – 4.09 (m, 1H), 3.78 – 3.67 (m, 2H), 3.63 – 3.50 (m, 2H), 3.42 – 3.11 (m, 4H), 3.00 – 2.89 (m, 3H), 2.70 (s, 6H), 2.57 – 2.44 (m, 4H), 2.37 – 2.27 (m, 2H), 2.17 – 2.08 (m, 1H), 1.92 – 1.76 (m, 2H), 1.60 – 1.47 (m, 3H), 1.42 – 1.23 (m, 4H), 1.16 – 1.06 (m, 1H), 0.95 – 0.87 (m, 6H), 0.79 – 0.42 (m, 1H).
386		645.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 1H), 7.45 – 7.32 (m, 1H), 7.13 – 7.09 (m, 1H), 7.06 – 6.84 (m, 3H),4.35 – 3.86 (m, 4H), 3.69 – 3.52 (m, 4H), 3.46 – 3.40 (m, 3H), 3.37 – 3.28 (m, 2H), 3.21 (br d, J = 11.4 Hz, 1H), 3.06 – 2.86 (m, 3H), 2.85 – 2.73 (m, 1H), 2.67 – 2.60 (m, 1H), 2.48 – 2.37 (m, 1H), 2.29 – 2.13 (m, 3H), 1.95 – 1.86 (m, 4H), 1.65 – 1.58(m, 1H), 1.29 – 1.03 (m, 7H), 0.86 (d, J = 6.9 Hz, 1H), 0.75 – 0.69 (m, 6H), 0.43 - -0.04 (m, 1H).
387		631.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 1H), 7.56 – 7.50 (m, 1H), 7.22 – 7.10 (m, 3H), 6.89 – 6.78 (m, 1H), 3.81 – 3.36 (m, 11H), 3.24 – 3.06 (m, 2H), 2.99 – 2.85 (m, 1H), 2.68 (s, 3H), 2.62 – 2.55 (m, 1H), 2.42 – 2.31 (m, 2H), 2.16 – 2.04 (m, 4H), 1.50 – 1.12 (m, 6H), 1.01 – 0.74 (m, 13H), 0.25 (dd, J = 3.6, 6.8 Hz, 2H).
388		590.7	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.87 (m, 1H), 7.74 – 7.59 (m, 1H), 7.43 – 7.24 (m, 2H), 7.08 – 6.96 (m, 1H), 6.87 – 6.68 (m, 1H), 4.59 – 4.49 (m, 4H), 3.60 – 3.36 (m, 4H), 3.19 – 3.14 (m, 4H), 3.13 – 2.88 (m, 3H), 2.68 – 2.52 (m, 3H), 2.27 – 2.17 (m, 2H), 2.01 – 1.92 (m, 1H), 1.74 – 1.63 (m, 1H), 1.30 – 1.03 (m, 5H), 0.92 – 0.87 (m, 2H), 0.86 – 0.70 (m, 10H), 0.32 - -0.15 (m, 3H).
390		604.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.31 (m, 2H), 7.77 – 7.55 (m, 2H), 7.26 – 6.89 (m, 4H), 4.64 – 3.65 (m, 8H), 3.55 – 3.32 (m, 4H), 3.05 – 2.82 (m, 5H), 2.70 (s, 3H), 2.49 – 2.29 (m, 1H), 2.23 – 1.55 (m, 8H), 1.38 – 1.14 (m, 1H), 1.13 – 0.76 (m, 12H), 0.31 – 0.22 (m, 2H).
391		622.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 14.8 Hz, 1H), 7.65 – 7.49 (m, 1H), 7.39 – 7.14 (m, 2H), 6.90 – 6.57 (m, 1H), 4.61 – 4.02 (m, 4H), 3.80 – 3.56 (m, 7H), 3.51 (d, J = 5.2 Hz, 2H), 3.27 – 3.20 (m, 2H), 3.18 – 2.88 (m, 2H), 2.68 (s, 2H), 2.60 (s, 3H), 2.25 (s, 1H), 1.87 (d, J = 8.4 Hz, 2H), 1.65 – 1.22 (m, 6H), 1.21 – 1.12 (m, 1H), 1.00 – 0.73 (m, 8H).
392		603.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 2H), 8.10 (s, 1H), 7.78 – 7.66 (m, 1H), 7.46 – 7.16 (m, 3H), 7.01 – 6.90 (m, 1H), 4.65 – 4.02 (m, 8H), 3.60 – 3.34 (m, 3H), 3.29 – 2.96 (m, 7H), 2.75 (s, 2H), 2.69 (s, 3H), 2.39 – 2.27 (m, 1H), 2.14 (s, 1H), 1.80 – 1.58 (m, 4H), 1.19 – 0.78 (m, 14H), 0.35 – 0.28 (m, 2H).

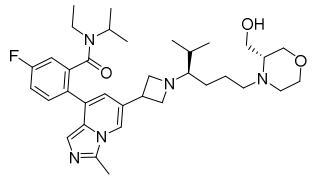
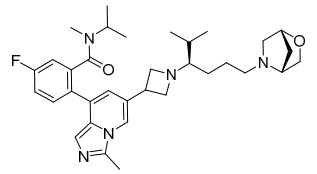
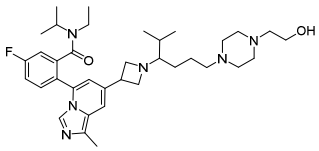
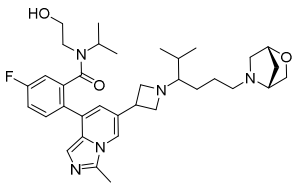
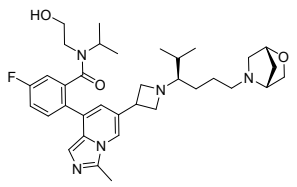
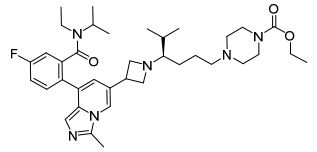
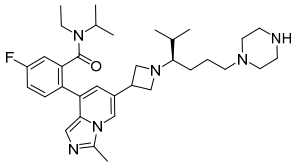
393		631.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 – 7.95 (m, 1H), 7.80 – 7.64 (m, 1H), 7.46 – 7.09 (m, 3H), 7.03 – 6.91 (m, 1H), 4.37 – 4.33 (m, 2H), 4.29 – 4.04 (m, 5H), 4.01 – 3.93 (m, 4H), 3.93 – 3.80 (m, 3H), 3.61 – 3.36 (m, 2H), 3.11 – 2.85 (m, 5H), 2.09 – 1.95 (m, 1H), 1.88 – 1.79 (m, 3H), 1.64 – 1.53 (m, 3H), 1.50 – 1.42 (m, 1H), 1.35 – 1.28 (m, 1H), 1.07 – 0.78 (m, 13H), 0.32 – 0.26 (m, 2H).
395		623.8	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.86 (m, 1H), 7.79 – 7.65 (m, 1H), 7.42 – 7.04 (m, 3H), 6.98 – 6.79 (m, 1H), 4.67 – 4.58 (m, 1H), 4.53 – 4.26 (m, 1H), 3.84 – 3.38 (m, 5H), 3.28 – 3.22 (m, 1H), 3.10 – 2.97 (m, 1H), 2.87 – 2.41 (m, 13H), 2.40 – 2.33 (m, 2H), 2.30 – 2.22 (m, 1H), 1.97 – 1.79 (m, 1H), 1.70 – 0.71 (m, 18H), 0.33 – 0.28 (m, 2H).
397		655.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.74 – 7.62 (m, 1H), 7.44 – 7.25 (m, 2H), 7.08 – 6.98 (m, 1H), 6.86 – 6.69 (m, 1H), 4.32 – 3.38 (m, 4H), 3.28 (s, 1H), 3.19 – 3.01 (m, 6H), 2.98 – 2.87 (m, 1H), 2.84 (s, 3H), 2.58 (s, 3H), 2.42 (s, 4H), 2.29 (s, 2H), 2.03 (s, 1H), 1.71 (s, 1H), 1.45 (s, 2H), 1.33 – 0.98 (m, 3H), 0.92 – 0.69 (m, 12H), 0.26 (br d, J = 6.4 Hz, 2H).
400-1		621.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.77 (m, 1H), 7.63 – 7.49 (m, 2H), 7.42 – 7.26 (m, 2H), 7.13 – 7.02 (m, 1H), 4.33 (t, J = 5.6 Hz, 1H), 4.04 (s, 3H), 3.69 – 3.60 (m, 3H), 3.48 – 3.36 (m, 3H), 3.31 – 3.24 (m, 1H), 3.20 – 3.06 (m, 2H), 2.88 – 2.75 (m, 1H), 2.42 – 2.24 (m, 9H), 2.23 – 2.18 (m, 2H), 2.06 – 1.99 (m, 1H), 1.79 – 1.67 (m, 1H), 1.50 – 1.37 (m, 2H), 1.31 – 1.16 (m, 2H), 1.07 – 0.59 (m, 14H), 0.11 – 0.05 (m, 2H).
400-2		621.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.59 – 7.52 (m, 1H), 7.25 – 7.12 (m, 3H), 4.10 (s, 3H), 3.93 – 3.76 (m, 3H), 3.61 (t, J = 5.2 Hz, 2H), 3.46 (td, J = 6.4, 13.2 Hz, 2H), 3.30 – 3.13 (m, 2H), 2.86 – 2.77 (m, 1H), 2.63 – 2.28 (m, 12H), 2.10 (br s, 1H), 1.97 – 1.76 (m, 3H), 1.62 – 1.49 (m, 2H), 1.44 – 1.23 (m, 2H), 1.13 – 0.67 (m, 13H), 0.06 (d, J = 6.8 Hz, 2H).
401-1		636.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.71 (m, 1H), 7.65 – 7.45 (m, 2H), 7.43 – 7.21 (m, 2H), 7.16 – 6.96 (m, 1H), 4.60 – 4.38 (m, 1H), 4.26 – 3.99 (m, 3H), 3.74 – 3.55 (m, 3H), 3.51 – 3.33 (m, 5H), 3.32 – 3.02 (m, 5H), 2.87 – 2.59 (m, 3H), 2.27 – 2.13 (m, 2H), 2.08 – 1.86 (m, 3H), 1.84 – 1.65 (m, 3H), 1.50 – 0.95 (m, 7H), 0.90 – 0.77 (m, 8H), 0.71 – 0.63 (m, 3H), 0.11 – 0.03 (m, 2H).
401-2		636.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.76 (m, 1H), 7.63 – 7.49 (m, 2H), 7.44 – 7.24 (m, 2H), 7.13 – 7.00 (m, 1H), 4.64 – 4.33 (m, 1H), 4.26 – 3.96 (m, 3H), 3.76 – 3.53 (m, 3H), 3.49 – 3.33 (m, 5H), 3.31 – 3.04 (m, 5H), 2.87 – 2.61 (m, 3H), 2.34 – 2.12 (m, 2H), 2.11 – 1.87 (m, 3H), 1.86 – 1.65 (m, 3H), 1.49 – 0.97 (m, 7H), 0.89 – 0.79 (m, 8H), 0.70 – 0.64 (m, 3H), 0.12 – 0.03 (m, 2H).
404		654.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.75 – 7.62 (m, 1H), 7.44 – 7.24 (m, 2H), 7.11 – 6.98 (m, 1H), 6.88 – 6.68 (m, 1H), 3.60 – 3.34 (m, 4H), 3.32 – 3.25 (m, 1H), 3.20 – 2.91 (m, 6H), 2.91 – 2.88 (m, 3H), 2.59 (s, 3H), 2.29 – 2.19 (m, 2H), 2.05 – 1.66 (m, 6H), 1.62 – 1.40 (m, 4H), 1.34 – 0.97 (m, 3H), 0.92 – 0.70 (m, 12H), 0.27 (d, J = 6.4

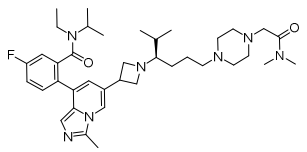
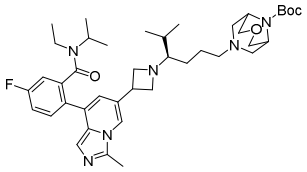
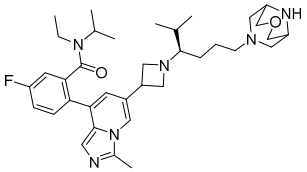
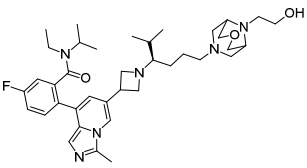
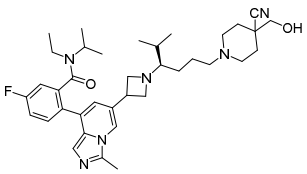
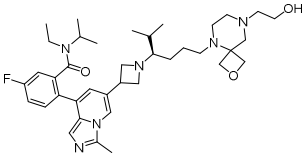
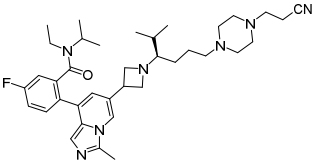
			Hz, 2H).
405		633.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.56 – 7.50 (m, 1H), 7.42 – 7.35 (m, 1H), 7.24 (dt, J = 2.8, 8.4 Hz, 1H), 7.17 – 7.08 (m, 1H), 7.06 (s, 1H), 3.98 (s, 3H), 3.84 – 3.69 (m, 3H), 3.59 – 3.48 (m, 1H), 3.38 (td, J = 6.8, 13.2 Hz, 1H), 3.33 – 3.22 (m, 2H), 3.22 – 3.18 (m, 6H), 2.88 – 2.76 (m, 3H), 2.26 (dt, J = 3.2, 8.0 Hz, 2H), 2.20 – 2.13 (m, 1H), 2.01 (t, J = 11.0 Hz, 2H), 1.58 – 1.13 (m, 7H), 0.97 (d, J = 7.2 Hz, 1H), 0.89 – 0.78 (m, 9H), 0.75 – 0.58 (m, 4H), -0.01 (d, J = 6.8 Hz, 2H).
406		654.4	^{1}H NMR (400 MHz, DMSO7.85 – 7.76 (m, 1H), 7.65 – 7.47 (m, 2H), 7.43 – 7.22 (m, 2H), 7.17 – 6.98 (m, 1H), 4.27 – 4.00 (m, 3H), 3.70 – 3.58 (m, 3H), 3.43 – 3.32 (m, 1H), 3.29 – 3.24 (m, 1H), 3.20 – 3.06 (m, 2H), 3.04 – 2.91 (m, 3H), 2.89 (s, 3H), 2.86 – 2.77 (m, 1H), 2.25 (t, J = 7.2 Hz, 2H), 2.07 – 2.00 (m, 1H), 1.98 – 1.83 (m, 4H), 1.79 – 1.68 (m, 1H), 1.62 – 1.40 (m, 4H), 1.32 – 1.16 (m, 2H), 1.04 – 0.61 (m, 13H), 0.08 (d, J = 6.4 Hz, 2H).
407		619.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.65 – 7.48 (m, 2H), 7.43 – 7.23 (m, 2H), 7.17 – 7.00 (m, 1H), 4.04 (s, 3H), 3.65 (s, 3H), 3.38 (s, 5H), 3.29 – 3.07 (m, 3H), 2.87 – 2.58 (m, 1H), 2.38 – 2.18 (m, 6H), 2.04 (s, 1H), 1.96 (s, 3H), 1.80 – 1.68 (m, 1H), 1.47 (s, 2H), 1.34 – 1.16 (m, 2H), 1.07 – 0.60 (m, 13H), 0.08 (d, J = 6.4 Hz, 2H).
409		631.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.79 (m, 1H), 7.65 – 7.50 (m, 2H), 7.44 – 7.26 (m, 2H), 7.14 – 7.02 (m, 1H), 4.11 (s, 2H), 4.07 – 4.02 (m, 3H), 3.83 (s, 2H), 3.69 – 3.59 (m, 3H), 3.41 – 3.35 (m, 1H), 3.30 – 3.22 (m, 1H), 3.19 – 3.08 (m, 6H), 2.88 – 2.76 (m, 1H), 2.31 – 2.21 (m, 2H), 2.03 – 1.96 (m, 1H), 1.76 – 1.68 (m, 4H), 1.26 – 1.14 (m, 3H), 1.04 – 0.64 (m, 14H), 0.10 – 0.04 (m, 2H).
410		623.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 1H), 7.54 – 7.44 (m, 1H), 7.28 – 7.21 (m, 1H), 7.19 – 7.02 (m, 3H), 4.56 (q, J = 4.4 Hz, 1H), 4.44 (q, J = 4.4 Hz, 1H), 4.04 (s, 3H), 3.94 – 3.13 (m, 6H), 2.86 – 2.22 (m, 13H), 1.91 – 1.60 (m, 4H), 1.46 – 1.17 (m, 3H), 1.08 – 0.59 (m, 13H), 0.04 -0.04 (m, 2H).
411		683.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 – 7.71 (m, 1H), 7.68 – 7.44 (m, 2H), 7.43 – 7.19 (m, 2H), 7.15 – 6.90 (m, 2H), 4.23 – 3.98 (m, 3H), 3.72 – 3.54 (m, 3H), 3.42 – 3.33 (m, 1H), 3.27 – 2.91 (m, 7H), 2.86 – 2.65 (m, 3H), 2.24 – 2.12 (m, 2H), 2.08 – 1.97 (m, 1H), 1.92 – 1.80 (m, 2H), 1.78 – 1.67 (m, 3H), 1.49 – 1.34 (m, 4H), 1.28 – 0.98 (m, 6H), 0.89 – 0.80 (m, 8H), 0.71 – 0.64 (m, 3H), 0.11 – 0.04 (m, 2H).
412		651.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 – 7.79 (m, 1H), 7.62 – 7.50 (m, 2H), 7.42 – 7.26 (m, 2H), 7.13 – 7.01 (m, 1H), 4.56 – 4.46 (m, 1H), 4.34 – 4.30 (m, 1H), 4.08 – 4.02 (m, 3H), 3.68 – 3.54 (m, 4H), 3.41 – 3.35 (m, 1H), 3.31 – 3.27 (m, 2H), 3.18 – 3.07 (m, 2H), 2.87 – 2.78 (m, 1H), 2.44 – 2.15 (m, 12H), 2.06 – 2.00 (m, 1H), 1.77 – 1.69 (m, 1H), 1.48 – 1.40 (m, 2H), 1.30 – 1.24 (m, 1H), 1.22 – 1.16 (m, 1H), 1.03 – 0.63 (m, 14H), 0.11 – 0.05 (m, 2H).

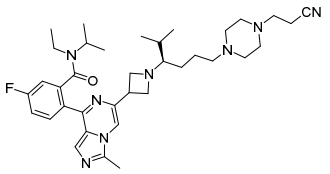
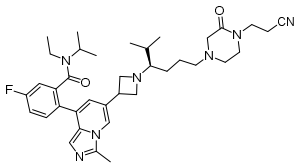
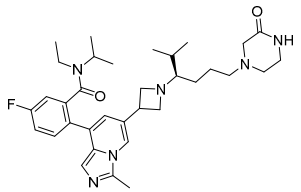
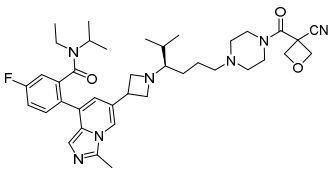
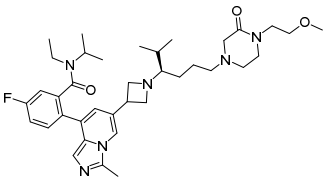
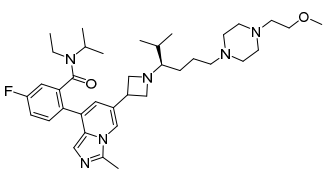
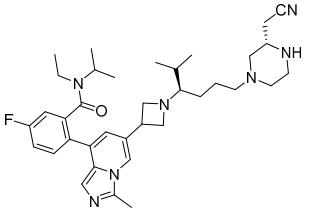
413		651.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.76 (m, 1H), 7.64 – 7.49 (m, 2H), 7.43 – 7.26 (m, 2H), 7.14 – 7.02 (m, 1H), 4.65 – 4.28 (m, 2H), 4.10 – 3.99 (m, 3H), 3.73 – 3.52 (m, 4H), 3.42 – 3.35 (m, 1H), 3.30 – 3.25 (m, 2H), 3.20 – 3.06 (m, 2H), 2.87 – 2.74 (m, 1H), 2.46 – 2.15 (m, 12H), 2.08 – 1.99 (m, 1H), 1.80 – 1.67 (m, 1H), 1.50 – 1.38 (m, 2H), 1.31 – 1.24 (m, 1H), 1.23 – 1.16 (m, 1H), 1.06 – 0.62 (m, 14H), 0.10 – 0.06 (m, 2H).
417		591.8	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.77 (m, 1H), 7.63 – 7.45 (m, 2H), 7.42 – 7.25 (m, 2H), 7.18 – 7.04 (m, 1H), 4.26 – 3.99 (m, 3H), 3.78 – 3.54 (m, 3H), 3.47 – 3.33 (m, 5H), 3.31 – 3.09 (m, 3H), 2.89 – 2.67 (m, 1H), 2.48 – 2.13 (m, 8H), 2.01 – 1.89 (m, 3H), 1.85 – 1.69 (m, 1H), 1.29 – 0.94 (m, 1H), 0.94 – 0.81 (m, 8H), 0.72 – 0.63 (m, 3H), 0.10 – 0.03 (m, 2H).
418		577.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.78 (m, 1H), 7.63 – 7.49 (m, 2H), 7.42 – 7.26 (m, 2H), 7.18 – 7.05 (m, 1H), 4.04 (s, 3H), 3.71 – 3.62 (m, 3H), 3.42 – 3.38 (m, 1H), 3.30 – 3.10 (m, 4H), 2.89 – 2.77 (m, 1H), 2.37 – 2.14 (m, 11H), 1.82 – 1.71 (m, 1H), 1.04 – 0.80 (m, 14H), 0.70 – 0.64 (m, 3H), 0.13 – 0.04 (m, 2H).
419		623.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.77 (m, 1H), 7.63 – 7.48 (m, 2H), 7.43 – 7.25 (m, 2H), 7.17 – 7.03 (m, 1H), 4.27 – 4.13 (m, 2H), 4.04 (s, 3H), 3.72 – 3.60 (m, 3H), 3.47 – 3.39 (m, 4H), 3.29 – 3.10 (m, 3H), 2.88 – 2.76 (m, 1H), 2.61 – 2.54 (m, 4H), 2.45 – 2.22 (m, 6H), 2.18 – 2.09 (m, 2H), 1.81 – 1.72 (m, 1H), 1.04 – 0.64 (m, 14H), 0.12 – 0.05 (m, 2H).
420		591.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (s, 1H), 7.67 – 7.59 (m, 1H), 7.54 – 7.46 (m, 1H), 7.38 – 7.30 (m, 1H), 7.27 – 7.14 (m, 2H), 4.09 (s, 3H), 3.93 – 3.76 (m, 3H), 3.55 – 3.34 (m, 2H), 2.98 – 2.21 (m, 16H), 1.95 – 1.82 (m, 1H), 1.67 – 1.53 (m, 2H), 1.49 – 1.26 (m, 2H), 1.13 – 0.69 (m, 14H), 0.10 (d, J = 6.8 Hz, 2H).
422		607.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.74 (m, 1H), 7.64 – 7.46 (m, 2H), 7.44 – 7.23 (m, 2H), 7.18 – 7.01 (m, 1H), 4.10 – 3.98 (m, 3H), 3.71 – 3.60 (m, 3H), 3.42 – 3.35 (m, 3H), 3.32 – 3.14 (m, 8H), 2.88 – 2.78 (m, 1H), 2.45 – 2.20 (m, 10H), 2.18 – 2.11 (m, 2H), 1.82 – 1.69 (m, 1H), 1.05 – 0.96 (m, 1H), 0.92 – 0.80 (m, 8H), 0.71 – 0.64 (m, 3H), 0.10 – 0.04 (m, 2H).
423		590.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.99 – 7.82 (m, 1H), 7.79 – 7.61 (m, 1H), 7.45 – 7.04 (m, 3H), 6.98 – 6.83 (m, 1H), 4.32 – 4.17 (m, 2H), 3.90 – 3.36 (m, 9H), 3.30 – 3.23 (m, 2H), 3.13 – 2.92 (m, 1H), 2.79 – 2.51 (m, 6H), 2.33 – 2.19 (m, 1H), 1.94 – 1.79 (m, 2H), 1.58 – 1.09 (m, 5H), 1.02 – 0.77 (m, 12H), 0.33 – 0.28 (m, 2H).
425		647.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 2H), 8.06 – 8.00 (m, 1H), 7.77 – 7.70 (m, 1H), 7.40 – 7.24 (m, 2H), 7.22 – 7.15 (m, 1H), 7.01 – 6.89 (m, 1H), 4.37 – 4.17 (m, 2H), 4.02 – 3.81 (m, 4H), 3.63 – 3.50 (m, 1H), 3.48 – 3.36 (m, 3H), 3.11 – 2.83 (m, 6H), 2.68 (s, 3H), 2.25 – 2.14 (m, 2H), 2.12 – 2.00 (m, 3H), 1.89 – 1.26 (m, 7H), 1.14 – 0.78 (m, 16H), 0.30 (d, J = 6.4 Hz, 2H).

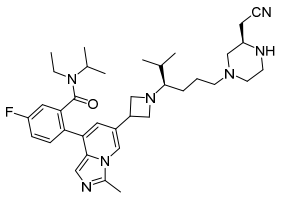
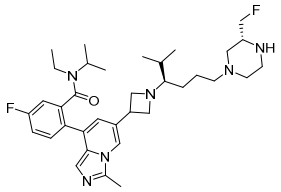
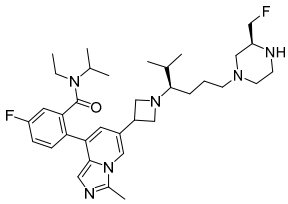
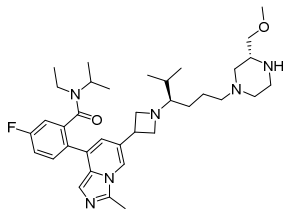
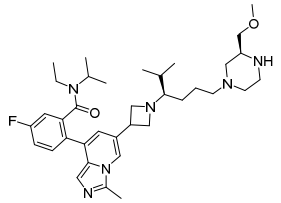
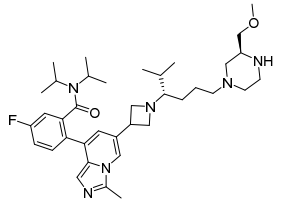
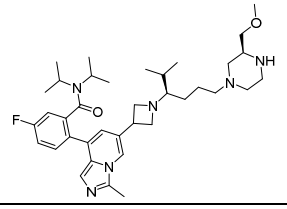
426		590.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.79 (m, 1H), 7.63 – 7.56 (m, 1H), 7.54 – 7.49 (m, 1H), 7.42 – 7.35 (m, 1H), 7.33 – 7.26 (m, 1H), 7.13 – 7.02 (m, 1H), 4.08 – 4.01 (m, 5H), 3.69 – 3.60 (m, 3H), 3.53 (d, J = 10.8 Hz, 2H), 3.41 – 3.33 (m, 4H), 3.31 – 3.25 (m, 1H), 3.19 – 3.07 (m, 2H), 2.87 – 2.78 (m, 1H), 2.41 (q, J = 6.4 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.77 – 1.64 (m, 2H), 1.40 – 1.22 (m, 4H), 1.05 – 0.80 (m, 10H), 0.72 – 0.62 (m, 4H), 0.07 (d, J = 5.6 Hz, 2H).
428		623.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 4.3 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.05 – 7.00 (m, 1H), 6.79 (d, J = 14.5 Hz, 1H), 4.50 (br s, 1H), 4.31 (dd, J = 2.3, 4.3 Hz, 1H), 3.67 – 3.37 (m, 5H), 3.31 – 2.88 (m, 6H), 2.58 (s, 3H), 2.47 – 2.07 (m, 13H), 1.72 (br d, J = 2.5 Hz, 1H), 1.07 – 0.71 (m, 13H), 0.26 (br d, J = 6.5 Hz, 2H).
429		623.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 4.0 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.05 – 7.00 (m, 1H), 6.90 – 6.76 (m, 1H), 4.54 – 4.46 (m, 1H), 4.35 – 4.28 (m, 1H), 3.62 – 3.37 (m, 5H), 3.31 – 2.85 (m, 6H), 2.58 (s, 3H), 2.48 – 2.09 (m, 13H), 1.79 – 1.66 (m, 1H), 1.08 – 0.71 (m, 13H), 0.26 (br d, J = 6.4 Hz, 2H).
430		607.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 3.6 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.41 – 7.28 (m, 2H), 7.07 – 7.01 (m, 1H), 6.91 – 6.77 (m, 1H), 3.63 – 3.34 (m, 6H), 3.31 – 2.88 (m, 6H), 2.59 (s, 3H), 2.46 – 2.10 (m, 13H), 1.81 – 1.66 (m, 1H), 1.08 – 0.72 (m, 13H), 0.27 (d, J = 6.4 Hz, 2H).
432		590.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.79 (m, 1H), 7.63 – 7.56 (m, 1H), 7.55 – 7.49 (m, 1H), 7.38 (dt, J = 2.8, 8.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.13 – 7.01 (m, 1H), 4.31 – 4.20 (m, 1H), 4.04 (s, 3H), 3.79 (d, J = 7.2 Hz, 1H), 3.68 – 3.60 (m, 3H), 3.48 – 3.43 (m, 1H), 3.39 (s, 1H), 3.20 – 3.06 (m, 2H), 2.88 – 2.77 (m, 1H), 2.72 (d, J = 9.6 Hz, 1H), 2.54 (s, 1H), 2.43 – 2.30 (m, 2H), 2.06 – 1.99 (m, 1H), 1.78 – 1.63 (m, 2H), 1.51 (d, J = 9.2 Hz, 1H), 1.45 – 1.17 (m, 5H), 1.05 – 0.96 (m, 1H), 0.88 – 0.81 (m, 9H), 0.71 – 0.62 (m, 4H), 0.07 (d, J = 6.4 Hz, 2H).
434		623.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.79 (m, 1H), 7.62 – 7.56 (m, 1H), 7.53 – 7.48 (m, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.26 (m, 1H), 7.11 – 7.05 (m, 1H), 4.54 – 4.46 (m, 1H), 4.35 – 4.28 (m, 1H), 4.07 – 4.00 (m, 3H), 3.72 – 3.61 (m, 3H), 3.58 – 3.52 (m, 1H), 3.42 – 3.35 (m, 1H), 3.30 – 3.23 (m, 4H), 3.23 – 3.17 (m, 1H), 2.89 – 2.77 (m, 1H), 2.70 – 2.55 (m, 1H), 2.44 – 2.24 (m, 9H), 2.20 – 2.14 (m, 3H), 1.82 – 1.70 (m, 1H), 0.92 – 0.88 (m, 3H), 0.84 (t, J = 6.8 Hz, 6H), 0.74 – 0.62 (m, 4H), 0.10 – 0.06 (m, 2H).
435		623.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.81 (m, 1H), 7.75 – 7.58 (m, 1H), 7.47 – 7.20 (m, 2H), 7.13 – 6.91 (m, 1H), 6.90 – 6.75 (m, 1H), 4.38 – 4.10 (m, 2H), 3.63 – 3.34 (m, 8H), 3.30 – 2.65 (m, 5H), 2.60 – 2.54 (m, 6H), 2.48 – 2.20 (m, 6H), 2.18 – 2.07 (m, 2H), 1.81 – 1.67 (m, 1H), 1.25 – 1.05 (m, 1H), 1.02 – 0.66 (m, 12H), 0.31 – 0.24 (m, 2H).

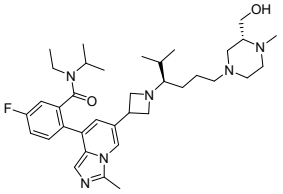
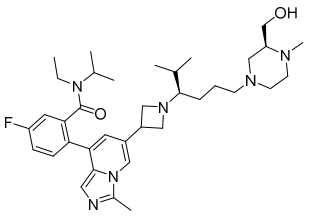
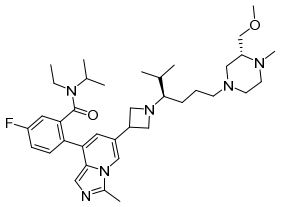
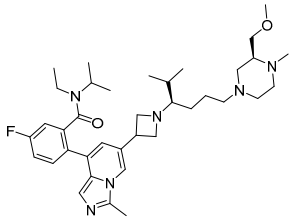
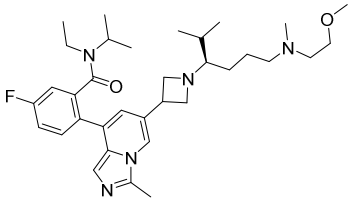
440		623.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 – 7.83 (m, 1 H), 7.56 – 7.62 (m, 1 H), 7.48 – 7.54 (m, 1 H), 7.39 (td, J=8.60, 2.80 Hz, 1 H), 7.26 – 7.34 (m, 1 H), 7.08 (d, J=13.20 Hz, 1 H), 4.51 (br s, 1 H), 4.32 (d, J=4.40 Hz, 1 H), 4.04 (s, 3 H), 3.62 – 3.70 (m, 3 H), 3.53 – 3.59 (m, 1 H), 3.37 (br d, J=6.80 Hz, 1 H), 3.26 – 3.31 (m, 3 H), 3.18 – 3.24 (m, 1 H), 2.83 (ddd, J=13.60, 6.80, 3.20 Hz, 1 H), 2.39 (br d, J=3.20 Hz, 5 H), 2.24 – 2.33 (m, 4 H), 2.10 – 2.23 (m, 4 H), 1.72 – 1.81 (m, 1 H), 1.01 (br d, J=6.00 Hz, 1 H), 0.88 – 0.92 (m, 3 H), 0.84 (t, J=6.80 Hz, 6 H), 0.68 (br t, J=6.80 Hz, 4 H), 0.08 (br d, J=6.40 Hz, 2 H).
442		627.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (d, J = 8.4 Hz, 1H), 7.78 – 7.67 (m, 1H), 7.40 – 7.19 (m, 2H), 7.17 – 7.08 (m, 1H), 7.03 – 6.86 (m, 1H), 3.93 – 3.79 (m, 1H), 3.77 – 3.62 (m, 2H), 3.60 – 3.35 (m, 3H), 3.28 – 3.23 (m, 2H), 3.21 – 3.17 (m, 2H), 3.11 – 2.94 (m, 1H), 2.81 (d, J = 10.0 Hz, 3H), 2.66 (s, 4H), 2.58 – 2.42 (m, 3H), 2.38 – 2.29 (m, 2H), 1.95 – 1.79 (m, 1H), 1.00 – 0.78 (m, 12H), 0.31 – 0.22 (m, 2H).
443		591.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.83 (m, 1H), 7.77 – 7.58 (m, 1H), 7.47 – 7.21 (m, 2H), 7.12 – 6.93 (m, 1H), 6.93 – 6.74 (m, 1H), 4.34 – 3.36 (m, 7H), 3.26 – 2.71 (m, 4H), 2.66 – 2.52 (m, 3H), 2.43 – 2.09 (m, 8H), 2.01 – 1.90 (m, 3H), 1.81 – 1.69 (m, 1H), 1.24 – 1.03 (m, 1H), 0.91 – 0.70 (m, 12H), 0.27 – 0.20 (m, 2H).
444		578.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J=5.20 Hz, 1 H), 7.67 (dd, J=8.00, 5.60 Hz, 1 H), 7.27 – 7.42 (m, 2 H), 6.99 – 7.06 (m, 1 H), 6.79 (d, J=14.01 Hz, 1 H), 3.53 – 3.63 (m, 2 H), 3.46 (td, J=13.20, 6.80 Hz, 2 H), 3.25 – 3.29 (m, 1 H), 3.19 (s, 4 H), 3.02 – 3.15 (m, 2 H), 2.88 – 2.99 (m, 1 H), 2.73 (br d, J=2.00 Hz, 1 H), 2.55 – 2.67 (m, 4 H), 2.24 (br s, 1 H), 2.13 (br s, 2 H), 2.00 – 2.09 (m, 1 H), 1.95 (br d, J=10.00 Hz, 1 H), 1.68 – 1.85 (m, 3 H), 1.29 – 1.47 (m, 2 H), 0.96 – 1.13 (m, 1 H), 0.86 – 0.91 (m, 5 H), 0.75 – 0.84 (m, 6 H), 0.73 (br t, J=6.80 Hz, 1 H), 0.26 (br d, J=6.40 Hz, 2 H).
450		608.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.73 – 7.63 (m, 1H), 7.42 – 7.27 (m, 2H), 7.07 – 7.00 (m, 1H), 6.86 – 6.71 (m, 1H), 4.61 (s, 1H), 4.35 – 3.68 (m, 1H), 3.60 – 3.34 (m, 7H), 3.31 – 2.74 (m, 6H), 2.59 (s, 4H), 2.30 – 2.16 (m, 2H), 2.08 – 2.00 (m, 1H), 1.98 – 1.87 (m, 1H), 1.77 – 1.61 (m, 2H), 1.53 – 1.38 (m, 2H), 1.34 – 0.97 (m, 3H), 0.92 – 0.71 (m, 12H), 0.28 (d, J = 6.4 Hz, 2H).
451		608.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 – 7.97 (m, 1H), 7.87 – 7.58 (m, 1H), 7.47 – 7.11 (m, 3H), 7.05 – 6.81 (m, 1H), 4.61 – 4.37 (m, 2H), 4.29 – 3.91 (m, 4H), 3.79 – 3.37 (m, 6H), 3.30 – 3.25 (m, 1H), 3.20 – 2.97 (m, 3H), 2.80 – 2.63 (m, 5H), 2.58 – 2.46 (m, 1H), 2.41 – 2.24 (m, 1H), 2.20 – 2.02 (m, 1H), 1.85 – 1.52 (m, 4H), 1.30 – 0.79 (m, 13H), 0.34 – 0.29 (m, 2H).
452		608.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 – 8.02 (m, 1H), 7.86 – 7.55 (m, 1H), 7.41 – 7.16 (m, 3H), 7.03 – 6.87 (m, 1H), 4.55 – 4.33 (m, 2H), 4.29 – 4.03 (m, 3H), 3.92 – 3.37 (m, 8H), 3.25 – 2.99 (m, 4H), 2.94 – 2.86 (m, 1H), 2.85 – 2.75 (m, 2H), 2.73 – 2.65 (m, 3H), 2.20 – 2.05 (m, 1H), 1.86 –

			1.55 (m, 4H), 1.15 – 0.78 (m, 13H), 0.34 – 0.28 (m, 2H).
453		608.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.88 (m, 1H), 7.77 – 7.68 (m, 1H), 7.38 – 7.31 (m, 1H), 7.29 – 7.21 (m, 1H), 7.17 – 7.12 (m, 1H), 6.96 – 6.85 (m, 1H), 3.87 – 3.35 (m, 12H), 3.28 – 3.22 (m, 1H), 3.11 – 2.97 (m, 1H), 2.85 – 2.71 (m, 2H), 2.69 – 2.64 (m, 3H), 2.50 – 2.32 (m, 3H), 2.26 (s, 1H), 1.94 – 1.80 (m, 1H), 1.71 – 1.38 (m, 3H), 1.34 – 1.06 (m, 2H), 0.99 – 0.77 (m, 12H), 0.30 (d, J = 6.4 Hz, 2H).
460		677.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.82 (m, 1H), 7.82 – 7.58 (m, 1H), 7.52 – 7.18 (m, 2H), 7.18 – 6.91 (m, 1H), 6.88 – 6.69 (m, 1H), 4.55 – 4.13 (m, 1H), 3.86 – 3.70 (m, 1H), 3.60 – 3.33 (m, 6H), 3.18 – 3.00 (m, 2H), 2.76 – 2.69 (m, 1H), 2.62 – 2.57 (m, 4H), 2.48 – 2.28 (m, 4H), 2.08 – 1.99 (m, 1H), 1.79 – 0.19 (m, 20H).
466		621.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.73 – 7.63 (m, 1H), 7.26 – 7.10 (m, 3H), 6.65 – 6.46 (m, 1H), 3.83 – 3.42 (m, 7H), 3.21 – 3.05 (m, 2H), 2.96 – 2.81 (m, 1H), 2.66 – 2.53 (m, 6H), 2.52 (s, 3H), 2.50 – 2.44 (m, 2H), 2.33 (br t, J = 7.6 Hz, 2H), 2.17 – 2.01 (m, 1H), 1.87 – 1.75 (m, 2H), 1.56 (br d, J = 4.0 Hz, 3H), 1.39 – 1.24 (m, 2H), 1.15 – 0.72 (m, 13H), 0.28 – 0.02 (m, 2H).
468		606.1	^{1}H NMR (400 MHz,CD_3OD) δ 7.96 – 7.86 (m, 1H), 7.79 – 7.65 (m, 1H), 7.41 – 7.22 (m, 2H), 7.21 – 7.10 (m, 1H), 6.97 – 6.82 (m, 1H), 4.58 (d, J = 5.2 Hz, 1H), 4.45 – 4.36 (m, 1H), 4.07 – 3.96 (m, 1H), 3.91 – 3.33 (m, 9H), 3.31 – 3.02 (m, 4H), 2.91 – 2.82 (m, 1H), 2.66 (s, 3H), 2.63 – 2.52 (m, 2H), 2.28 (d, J = 4.0 Hz, 1H), 1.98 – 1.81 (m, 2H), 1.79 – 1.69 (m, 1H), 1.68 – 1.51 (m, 2H), 1.47 – 1.10 (m, 3H), 1.06 – 0.87 (m, 9H), 0.35 – 0.25 (m, 2H).
468-1		606.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.80 (m, 1H), 7.77 – 7.52 (m, 1H), 7.46 – 7.21 (m, 2H), 7.12 – 6.87 (m, 1H), 6.83 – 6.62 (m, 1H), 4.75 – 4.54 (m, 1H), 4.31 – 4.16 (m, 1H), 3.84 – 3.73 (m, 1H), 3.61 – 3.41 (m, 7H), 3.19 – 3.03 (m, 3H), 3.00 – 2.83 (m, 2H), 2.76 – 2.69 (m, 1H), 2.62 – 2.56 (m, 3H), 2.45 – 2.38 (m, 1H), 2.37 – 2.31 (m, 1H), 2.08 – 2.00 (m, 1H), 1.76 – 1.64 (m, 2H), 1.55 – 1.48 (m, 1H), 1.46 – 1.34 (m, 2H), 1.33 – 1.16 (m, 3H), 1.05 – 0.78 (m, 10H), 0.29 – 0.21 (m, 2H).
471		649.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 – 7.64 (m, 1H), 7.42 – 7.27 (m, 2H), 7.07 – 7.00 (m, 1H), 6.75 (d, J = 15.6 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.58 – 3.40 (m, 4H), 3.32 – 3.26 (m, 5H), 3.17 – 3.03 (m, 2H), 2.97 – 2.87 (m, 1H), 2.58 (s, 3H), 2.32 – 2.21 (m, 6H), 2.08 – 1.99 (m, 1H), 1.76 – 1.66 (m, 1H), 1.52 – 1.39 (m, 2H), 1.30 – 1.19 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H), 0.99 – 0.69 (m, 13H), 0.27 (d, J = 6.4 Hz, 2H).
472		577.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.67 (dd, J = 5.6, 8.4 Hz, 1H), 7.43 – 7.26 (m, 2H), 7.08 – 6.99 (m, 1H), 6.75 (d, J = 18.4 Hz, 1H), 3.62 – 3.39 (m, 6H), 3.34 – 3.26 (m, 1H), 3.16 – 3.01 (m, 2H), 2.92 (dd, J = 6.8, 13.6 Hz, 1H), 2.64 (s, 3H), 2.58 (s, 3H), 2.34 – 2.13 (m, 6H), 2.02 (s, 1H), 1.77 – 1.65 (m, 1H), 1.43 (s, 2H), 1.31 – 0.99 (m, 3H), 0.92 – 0.71 (m, 12H), 0.27 (d, J = 6.4 Hz, 2H).

473		662.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.88 (m, 1H), 7.71 – 7.62 (m, 1H), 7.41 – 7.26 (m, 2H), 7.06 – 6.99 (m, 1H), 6.87 – 6.70 (m, 1H), 3.59 – 3.40 (m, 4H), 3.34 – 3.25 (m, 2H), 3.19 – 3.02 (m, 4H), 2.99 (s, 3H), 2.95 – 2.86 (m, 1H), 2.78 (s, 3H), 2.58 (s, 3H), 2.43 – 2.16 (m, 9H), 2.08 – 1.99 (m, 1H), 1.78 – 1.64 (m, 1H), 1.52 – 1.35 (m, 2H), 1.29 – 0.70 (m, 15H), 0.27 (d, J = 6.4 Hz, 2H).
478		719.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.79 (m, 1H), 7.74 – 7.55 (m, 1H), 7.47 – 7.21 (m, 2H), 7.16 – 6.93 (m, 1H), 6.89 – 6.60 (m, 1H), 3.87 – 3.76 (m, 2H), 3.65 (br s, 2H), 3.61 – 3.36 (m, 7H), 3.20 – 3.00 (m, 2H), 2.99 – 2.80 (m, 3H), 2.62 – 2.56 (m, 3H), 2.24 – 2.08 (m, 4H), 2.03 (br s, 1H), 1.77 – 1.65 (m, 1H), 1.54 – 1.34 (m, 11H), 1.32 – 1.01 (m, 3H), 0.97 – 0.69 (m, 12H), 0.32 – 0.24 (m, 2H).
479		619.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.84 (m, 1H), 7.75 – 7.57 (m, 1H), 7.46 – 7.16 (m, 2H), 7.12 – 6.94 (m, 1H), 6.89 – 6.53 (m, 1H), 3.70 – 3.45 (m, 9H), 3.20 – 3.00 (m, 3H), 2.96 – 2.79 (m, 3H), 2.71 – 2.65 (m, 2H), 2.61 – 2.56 (m, 3H), 2.26 – 2.09 (m, 4H), 2.07 – 1.99 (m, 1H), 1.78 – 1.65 (m, 1H), 1.51 – 1.38 (m, 2H), 1.31 – 1.06 (m, 3H), 0.95 – 0.71 (m, 12H), 0.31 – 0.25 (m, 2H)
480		663.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.78 – 7.55 (m, 1H), 7.47 – 7.18 (m, 2H), 7.15 – 6.92 (m, 1H), 6.87 – 6.65 (m, 1H), 4.36 – 4.24 (m, 1H), 3.84 – 3.71 (m, 2H), 3.62 – 3.39 (m, 9H), 3.19 – 3.02 (m, 2H), 2.98 – 2.85 (m, 1H), 2.75 – 2.69 (m, 2H), 2.66 – 2.55 (m, 7H), 2.46 – 2.35 (m, 2H), 2.18 – 2.07 (m, 2H), 2.06 – 1.99 (m, 1H), 1.80 – 1.62 (m, 1H), 1.52 – 1.37 (m, 2H), 1.33 – 0.99 (m, 3H), 0.93 – 0.70 (m, 12H), 0.30 – 0.25 (m, 2H).
481		631.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1 H), 7.63 – 7.72 (m, 1 H), 7.28 – 7.41 (m, 2 H), 7.00 – 7.07 (m, 1 H), 6.75 (d, J=17.60 Hz, 1 H), 5.38 (t, J=5.60 Hz, 1 H), 3.47 – 3.59 (m, 3 H), 3.43 (br d, J=4.00 Hz, 2 H), 3.26 – 3.31 (m, 1 H), 3.02 – 3.18 (m, 2 H), 2.92 (dq, J=13.60, 6.40 Hz, 1 H), 2.83 (br d, J=11.20 Hz, 2 H), 2.59 (s, 3 H), 2.23 – 2.31 (m, 2 H), 1.98 – 2.07 (m, 3 H), 1.67 – 1.81 (m, 3 H), 1.38 – 1.50 (m, 4 H), 1.01 – 1.32 (m, 3 H), 0.70 – 0.95 (m, 13 H), 0.27 (d, J=6.80 Hz, 2 H).
482		663.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.70 – 7.64 (m, 1H), 7.42 – 7.33 (m, 1H), 7.33 – 7.28 (m, 1H), 7.06 – 7.01 (m, 1H), 6.75 (d, J = 15.6 Hz, 1H), 4.53 (d, J = 6.4 Hz, 2H), 4.38 (t, J = 5.2 Hz, 1H), 4.15 (d, J = 6.4 Hz, 2H), 3.61 – 3.41 (m, 6H), 3.30 – 3.27 (m, 1H), 3.19 – 3.03 (m, 2H), 2.97 – 2.89 (m, 1H), 2.64 – 2.53 (m, 7H), 2.45 – 2.39 (m, 2H), 2.38 – 2.30 (m, 4H), 2.08 – 2.00 (m, 1H), 1.77 – 1.66 (m, 1H), 1.52 – 1.39 (m, 2H), 1.34 – 1.21 (m, 2H), 0.94 – 0.70 (m, 13H), 0.30 – 0.24 (m, 2H).
489		630.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.78 – 7.58 (m, 1H), 7.46 – 7.24 (m, 2H), 7.07 – 6.98 (m, 1H), 6.88 – 6.65 (m, 1H), 3.60 – 3.40 (m, 4H), 3.30 – 2.84 (m, 4H), 2.67 – 2.52 (m, 7H), 2.45 – 2.28 (m, 7H), 2.26 – 2.19 (m, 2H), 2.07 – 1.99 (m, 1H), 1.76 – 1.66 (m, 1H), 1.52 – 1.36 (m, 2H), 1.29 – 1.03 (m, 3H), 0.99 – 0.67 (m, 13H), 0.31 – 0.24 (m, 2H)

492		631.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 1H), 7.63 – 7.57 (m, 1H), 7.47 (s, 1H), 7.26 – 7.11 (m, 2H), 4.49 – 3.83 (m, 1H), 3.75 – 3.61 (m, 3H), 3.36 – 3.14 (m, 4H), 2.75 – 2.69 (m, 2H), 2.68 (s, 3H), 2.55 – 2.43 (m, 8H), 2.31 (br t, J = 7.2 Hz, 2H), 2.14 – 2.09 (m, 1H), 2.06 – 1.92 (m, 3H), 1.85 – 1.75 (m, 1H), 1.61 – 1.47 (m, 2H), 1.37 – 1.22 (m, 2H), 1.13 – 1.05 (m, 3H), 1.04 – 0.99 (m, 3H), 0.94 – 0.82 (m, 8H).
493		644.4	^{1}H NMR (400 MHz,CD_3OD) δ 8.36 (s, 1H), 8.11 – 7.99 (m, 1H), 7.82 – 7.59 (m, 1H), 7.41 – 7.18 (m, 3H), 7.05 – 6.76 (m, 1H), 4.57 – 4.42 (m, 2H), 4.36 – 4.17 (m, 2H), 4.16 – 3.99 (m, 1H), 3.67 – 3.32 (m, 7H), 3.23 – 2.97 (m, 3H), 2.89 – 2.64 (m, 7H), 2.60 – 2.42 (m, 2H), 2.21 – 2.07 (m, 1H), 1.78 – 1.54 (m, 4H), 1.14 – 0.79 (m, 13H), 0.35 – 0.28 (m, 2H).
494		591.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.74 – 7.62 (m, 2H), 7.43 – 7.25 (m, 2H), 7.06 – 7.00 (m, 1H), 6.84 – 6.71 (m, 1H), 3.60 – 3.42 (m, 6H), 3.17 – 3.03 (m, 4H), 2.95 – 2.85 (m, 3H), 2.60 – 2.57 (m, 3H), 2.34 – 2.27 (m, 2H), 2.06 – 2.01 (m, 1H), 1.76 – 1.66 (m, 1H), 1.52 – 1.40 (m, 2H), 1.31 – 1.04 (m, 3H), 0.96 – 0.70 (m, 13H), 0.30 – 0.26 (m, 2H).
495		686.5	^{1}H NMR (400 MHz,DMSO-d_6) δ 7.93 (s, 1H), 7.75 – 7.65 (m, 1H), 7.44 – 7.28 (m, 2H), 7.09 – 6.99 (m, 1H), 6.87 – 6.73 (m, 1H), 5.01 – 4.92 (m, 4H), 3.60 – 3.43 (m, 6H), 3.21 – 2.89 (m, 5H), 2.59 (s, 3H), 2.43 – 2.26 (m, 6H), 2.09 – 2.00 (m, 1H), 1.77 – 1.67 (m, 1H), 1.56 – 1.40 (m, 2H), 1.33 – 1.16 (m, 2H), 1.16 – 0.66 (m, 14H), 0.27 (m, 2H).
496		649.5	**^{1}H NMR** (400 MHz, DMSO-*d*6) δ = 7.93 (s, 1H), 7.73 – 7.64 (m, 1H), 7.41 – 7.27 (m, 2H), 7.06 – 7.01 (m, 1H), 6.85 – 6.72 (m, 1H), 3.59 – 3.40 (m, 8H), 3.31 – 3.28 (m, 2H), 3.22 (s, 3H), 3.17 – 3.04 (m, 2H), 2.97 – 2.88 (m, 3H), 2.58 (s, 5H), 2.34 – 2.25 (m, 2H), 2.07 – 2.01 (m, 1H), 1.77 – 1.68 (m, 1H), 1.51 – 1.41 (m, 2H), 1.33 – 0.68 (m, 16H), 0.29 – 0.25 (m, 2H)
497		635.4	^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (s, 1H), 7.72 – 7.64 (m, 1H), 7.38 (dt, J = 2.8, 8.4 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.07 – 7.01 (m, 1H), 6.76 (d, J = 17.2 Hz, 1H), 3.60 – 3.43 (m, 4H), 3.42 – 3.38 (m, 2H), 3.30 (br s, 1H), 3.21 (s, 3H), 3.18 – 3.04 (m, 2H), 2.99 – 2.88 (m, 1H), 2.59 (s, 3H), 2.44 – 2.26 (m, 9H), 2.21 (br t, J = 6.8 Hz, 2H), 2.08 – 2.00 (m, 1H), 1.77 – 1.68 (m, 1H), 1.52 – 1.37 (m, 2H), 1.30 – 1.16 (m, 2H), 1.14 – 1.00 (m, 1H), 0.97 – 0.68 (m, 13H), 0.29 (br d, J = 6.4 Hz, 2H)
498		616.4	^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.92 (s, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.26 (m, 2H), 7.06 – 6.99 (m, 1H), 6.85 – 6.70 (m, 1H), 3.62 – 3.38 (m, 5H), 3.32 – 2.60 (m, 9H), 2.58 (s, 3H), 2.56 – 2.52 (m, 2H), 2.25 – 2.18 (m, 2H), 2.05 – 1.99 (m, 1H), 1.88 (t, J = 10.0 Hz, 1H), 1.71 (t, J = 7.2 Hz, 2H), 1.51 – 1.36 (m, 2H), 1.30 – 1.14 (m, 2H), 1.10 – 0.70 (m, 13H), 0.28 (d, J = 6.0 Hz, 2H)

499		616.5	^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.92 (s, 1H), 7.75 – 7.59 (m, 1H), 7.51 – 7.20 (m, 2H), 7.09 – 6.96 (m, 1H), 6.86 – 6.70 (m, 1H), 3.61 – 3.40 (m, 4H), 3.30 – 3.01 (m, 3H), 2.95 – 2.52 (m, 12H), 2.25 – 2.19 (m, 2H), 2.06 – 2.00 (m, 1H), 1.93 – 1.83 (m, 1H), 1.79 – 1.63 (m, 2H), 1.50 – 1.37 (m, 2H), 1.34 – 0.99 (m, 3H), 0.92 – 0.71 (m, 12H), 0.31 – 0.25 (m, 2H)
500		609.5	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.01 – 7.84 (m, 1H), 7.74 – 7.63 (m, 1H), 7.45 – 7.25 (m, 2H), 7.08 – 6.99 (m, 1H), 6.86 – 6.69 (m, 1H), 4.46 – 4.24 (m, 2H), 3.68 – 3.48 (m, 4H), 3.15 – 2.66 (m, 9H), 2.63 – 2.55 (m, 3H), 2.34 – 2.24 (m, 2H), 2.18 – 2.07 (m, 1H), 2.03 – 1.94 (m, 1H), 1.87 – 1.67 (m, 2H), 1.52 – 1.05 (m, 6H), 0.92 – 0.71 (m, 12H), 0.30 – 0.22 (m, 2H)
501		609.5	^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.92 (s, 1H), 7.72 – 7.63 (m, 1H), 7.42 – 7.26 (m, 2H), 7.08 – 6.98 (m, 1H), 6.85 – 6.69 (m, 1H), 4.38 – 4.19 (m, 2H), 3.60 – 3.40 (m, 4H), 3.18 – 2.74 (m, 6H), 2.73 – 2.60 (m, 3H), 2.58 (s, 3H), 2.25 – 2.17 (m, 2H), 2.03 (s, 1H), 1.88 (t, J = 10.0 Hz, 1H), 1.76 – 1.62 (m, 2H), 1.52 – 0.93 (m, 6H), 0.92 – 0.71 (m, 12H), 0.28 (d, J = 6.4 Hz, 2H)
502		621.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1 H), 7.63 – 7.74 (m, 1 H), 7.26 – 7.41 (m, 2 H), 6.99 – 7.07 (m, 1 H), 6.75 (d, *J*=17.20 Hz, 1 H), 3.42 – 3.62 (m, 5 H), 3.30 (br s, 1 H), 3.15 – 3.24 (m, 6 H), 3.03 – 3.13 (m, 2 H), 2.92 (td, *J*=13.60, 6.40 Hz, 1 H), 2.75 – 2.81 (m, 2 H), 2.57 – 2.70 (m, 6 H), 2.20 (br t, *J*=7.20 Hz, 2 H), 2.02 (br s, 1 H), 1.80 – 1.91 (m, 1 H), 1.68 – 1.76 (m, 1 H), 1.54 – 1.63 (m, 1 H), 1.35 – 1.50 (m, 2 H), 1.13 – 1.29 (m, 2 H), 0.90 (br d, *J*=6.40 Hz, 2 H), 0.69 – 0.87 (m, 10 H), 0.28 (br d, *J*=6.40 Hz, 2 H)
503		621.5	^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (s, 1H), 7.77 – 7.59 (m, 1H), 7.50 – 7.17 (m, 2H), 7.13 – 6.93 (m, 1H), 6.90 – 6.65 (m, 1H), 3.61 – 3.39 (m, 5H), 3.27 – 3.03 (m, 8H), 2.98 – 2.87 (m, 1H), 2.86 – 2.78 (m, 2H), 2.73 – 2.55 (m, 6H), 2.28 – 2.13 (m, 2H), 2.08 – 1.98 (m, 1H), 1.93 – 1.82 (m, 1H), 1.76 – 1.58 (m, 2H), 1.52 – 1.35 (m, 2H), 1.31 – 0.99 (m, 3H), 0.93 – 0.71 (m, 12H), 0.31 – 0.24 (m, 2H)
505-1		635.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.85 (m, 1H), 7.69 – 7.62 (m, 1H), 7.40 – 7.31 (m, 1H), 7.26 – 7.21 (m, 1H), 7.04 – 7.00 (m, 1H), 6.83 – 6.73 (m, 1H), 3.60 – 3.34 (m, 5H), 3.29 – 3.24 (m, 1H), 3.22 – 3.19 (m, 3H), 3.19 – 3.10 (m, 3H), 3.09 – 3.01 (m, 1H), 2.80 – 2.71 (m, 2H), 2.68 – 2.57 (m, 6H), 2.23 – 2.14 (m, 2H), 2.03 – 1.97 (m, 1H), 1.88 – 1.78 (m, 1H), 1.76 – 1.65 (m, 1H), 1.62 – 1.52 (m, 1H), 1.49 – 1.34 (m, 5H), 1.28 – 1.13 (m, 2H), 1.10 – 1.03 (m, 3H), 0.94 – 0.88 (m, 3H), 0.87 – 0.79 (m, 6H), 0.28 – 0.17 (m, 3H).
505-2		635.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.89 (m, 1H), 7.70 – 7.62 (m, 1H), 7.39 – 7.30 (m, 1H), 7.27 – 7.18 (m, 1H), 7.06 – 6.99 (m, 1H), 6.84 – 6.72 (m, 1H), 3.59 – 3.38 (m, 5H), 3.29 – 3.25 (m, 1H), 3.22 – 3.19 (m, 3H), 3.19 – 3.10 (m, 3H), 3.08 – 3.01 (m, 1H), 2.80 – 2.71 (m, 2H), 2.69 – 2.58 (m, 6H), 2.23 – 2.15 (m, 2H), 2.03 – 1.98 (m, 1H),

			1.88 – 1.79 (m, 1H), 1.76 – 1.66 (m, 1H), 1.57 (dt, J = 4.4, 10.0 Hz, 1H), 1.49 – 1.35 (m, 5H), 1.29 – 1.05 (m, 5H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 – 0.79 (m, 6H), 0.23 (d, J = 6.4 Hz, 3H).
506		621.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 5.4, 8.4 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.22 – 7.11 (m, 3H), 6.91 – 6.78 (m, 1H), 3.97 – 3.86 (m, 1H), 3.82 – 3.66 (m, 2H), 3.66 – 3.41 (m, 4H), 3.26 – 3.07 (m, 2H), 2.99 – 2.71 (m, 4H), 2.68 (s, 3H), 2.51 – 2.42 (m, 1H), 2.34 (s, 3H), 2.34 – 2.07 (m, 6H), 1.87 – 1.79 (m, 1H), 1.61 – 1.51 (m, 2H), 1.40 – 1.12 (m, 3H), 1.04 – 0.75 (m, 13H), 0.25 (d, J = 6.8 Hz, 2H)
507		621.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.89 (m, 1H), 7.67 (dd, J = 5.6, 8.4 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.30 (dd, J = 2.8, 9.2 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.74 (d, J = 16.4 Hz, 1H), 4.51 – 4.21 (m, 1H), 3.59 – 3.44 (m, 5H), 3.25 – 3.03 (m, 4H), 2.93 (qd, J = 6.8, 13.6 Hz, 1H), 2.81 (br d, J = 10.4 Hz, 1H), 2.62 (br s, 1H), 2.59 (s, 4H), 2.22 – 2.17 (m, 2H), 2.15 (s, 3H), 2.11 (br dd, J = 8.8, 10.8 Hz, 1H), 2.04 – 2.00 (m, 1H), 1.99 – 1.92 (m, 2H), 1.76 – 1.67 (m, 2H), 1.50 – 1.38 (m, 2H), 1.31 – 1.08 (m, 3H), 0.93 – 0.76 (m, 12H), 0.31 – 0.27 (m, 2H)
508		635.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1 H), 7.61 – 7.74 (m, 1 H), 7.25 – 7.44 (m, 2 H), 7.00 – 7.09 (m, 1 H), 6.75 (d, J=17.20 Hz, 1 H), 3.38 – 3.62 (m, 5 H), 3.25 – 3.32 (m, 2 H), 3.04 – 3.22 (m, 6 H), 2.86 – 2.99 (m, 1 H), 2.66 – 2.75 (m, 1 H), 2.55 – 2.65 (m, 5 H), 2.06 – 2.23 (m, 7 H), 1.93 – 2.05 (m, 2 H), 1.67 – 1.80 (m, 2 H), 1.35 – 1.48 (m, 2 H), 1.13 – 1.29 (m, 2 H), 0.90 (br d, J=6.40 Hz, 2 H), 0.69 – 0.87 (m, 10 H), 0.28 (br d, J=6.40 Hz, 2 H)
509		635.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.97 – 7.86 (m, 1H), 7.78 – 7.67 (m, 1H), 7.38 – 7.29 (m, 1H), 7.27 – 7.21 (m, 1H), 7.16 – 7.12 (m, 1H), 6.94 – 6.86 (m, 1H), 3.82 – 3.32 (m, 8H), 3.30 – 3.22 (m, 4H), 3.14 – 2.97 (m, 1H), 2.95 – 2.75 (m, 3H), 2.73 – 2.59 (m, 3H), 2.42 – 2.21 (m, 8H), 2.20 – 2.11 (m, 1H), 2.05 – 1.94 (m, 1H), 1.92 – 1.81 (m, 1H), 1.69 – 1.51 (m, 2H), 1.47 – 1.10 (m, 3H), 1.02 – 0.75 (m, 12H), 0.33 – 0.27 (m, 2H)
510		580.5	^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.86 (m, 1H), 7.75 – 7.65 (m, 1H), 7.37 – 7.27 (m, 1H), 7.26 – 7.17 (m, 1H), 7.16 – 7.07 (m, 1H), 6.94 – 6.84 (m, 1H), 3.82 – 3.35 (m, 7H), 3.31 – 3.20 (m, 4H), 3.18 – 2.69 (m, 2H), 2.65 (s, 3H), 2.62 – 2.56 (m, 2H), 2.41 (q, J = 7.2 Hz, 2H), 2.31 – 2.20 (m, 4H), 1.93 – 1.78 (m, 1H), 1.66 – 1.48 (m, 2H), 1.44 – 1.08 (m, 3H), 0.97 – 0.75 (m, 12H), 0.29 (d, J = 5.6 Hz, 2H)

Activity Assay Examples

Experimental Example 1: Evaluation of Inhibitory Activity of Compounds Against Menin-MLL Binding

Reagents and Instruments:

His-Menin (M1-L615 end), purchased from BIORTUS, Catalog Number: BP9210; and

FITC-MLL4-43, purchased from GenScript, Catalog Number: C491HFF190-3/PE1324.

Experimental method:

In a 10 μL reaction solution (20 mM HEPES, pH 7.5, 50 mM NaCl, 1 mM DTT, 0.01% BSA) containing any compound from the examples, 150 nM His-Menin was added to a 384-well plate (Corning, Model: 4514). Each concentration was set up in duplicate wells. After centrifugation at 1000 RPM for 1 min, the plate was incubated at

25°C for 15 min. Then, 15 nM FITC-MLL1$_{4\text{-}43}$ (20 mM HEPES, pH 7.5, 50 mM NaCl, 1 mM DTT, 0.01% BSA) was added to a 384-well plate. After centrifugation at 1000 RPM for 1 min, the reaction proceeded at 25°C for 60 min. Changes in fluorescence polarization were measured using a plate reader (PerkinElmer, Envision 2104). Based on the measured signals, the binding inhibition rate of the compound at each concentration was calculated, and the IC50 (half-maximal inhibitory concentration) of the compound was determined using statistical analysis software GraphPad Prism (GraphPad Software, Inc.) by means of a nonlinear fitting formula: 4-Parameter Logistic Model or Sigmoidal Dose-Response Model:

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{(LogIC_{50} - X) \times Hill\ Slope}},$$

in which X indicates the logarithm of compound concentration, Y indicates a fluorescence polarization mP value, and Top and Bottom indicate the maximum and minimum readouts of fluorescence polarization mP values.
Experimental results are shown in Table 1.

Table 1: Inhibitory Activity of Compounds Against Menin-MLL Binding

Example	Menin-MLL IC_{50} (nM)	Example	Menin-MLL IC_{50} (nM)	Example	Menin-MLL IC_{50} (nM)	Example	Menin-MLL IC_{50} (nM)
4	**17.5**	163-2	**54.0**	281	**7.0**	394-2	**3.2**
11	**155**	164	**6.0**	281-1	**9.0**	395	**2.0**
11-1	**744**	165	**177**	281-2	**79.0**	396	**3.0**
11-2	**65.5**	165-1	**122**	282	**4.0**	397	**4.2**
15	**11.5**	165-2	**262**	282-1	**9.0**	398	**1.9**
16	**14.5**	166	**271**	282-2	**1.0**	399-1	**110**
17	**9.5**	166-1	**231**	283-1	**20.0**	399-2	**3.3**
18-1	**6.0**	166-2	**248**	283-2	**2.0**	400-1	**220**
18-2	**5.5**	167	**57.0**	284-1	**39.0**	400-2	**3.7**
19	**43.5**	168	**32.5**	284-2	**2.0**	401-1	**130**
20	**45.0**	170	**60.0**	285	**4.0**	401-2	**3.7**
21	**18.5**	171	**86.0**	286	**3.5**	402-1	**110**
22	**25.0**	172	**98.0**	287	**6.0**	402-2	**10.0**
22-1	**23.0**	173	**118**	288	**6.0**	403-1	**3.9**
22-2	**14.0**	174	**125**	288-1	**11.0**	403-2	**10.0**
23	**102**	175	**138**	288-2	**2.0**	404	**2.3**
24	**23.0**	176	**424**	289	**10.0**	405	**1.6**
25	**19.0**	177	**217**	290	**4.0**	406	**7.0**
25-1	**5.7**	178	**115**	291	**3.0**	407	**33.0**
25-2	**21.0**	179	**89.0**	291-1	**6.0**	408	**1.7**
26	**44.5**	180	**22.0**	292	**4.5**	409	**4.0**
28	**118**	181-1	**621**	293	**3.1**	410	**5.8**
29	**10.5**	181-2	**13.5**	294	**9.5**	411	**2.7**
30	**6.0**	182-1	**824**	295	**5.0**	412	**6.8**
31	**275**	182-2	**13.0**	296-1	**1.0**	413	**6.9**
34	**168**	183-1	**507**	296-2	**3.0**	414	**11.8**
35	**39.5**	183-2	**11.7**	297-1	**10.8**	415	**160.0**
36	**156**	184-1	**805**	297-2	**13.5**	416-1	**150**
38	**128**	184-2	**13.0**	298	**14.5**	416-2	**10.6**
39	**137**	185	**14.5**	299	**15.0**	417	**62.0**
40	**83.0**	186-1	**262**	300	**24.0**	418	**6.3**
41	**92.0**	186-2	**5.2**	301	**9.0**	419	**8.1**

42	**3.5**	187	**16.5**	302	**22.0**	420	**3.8**
44	**29.5**	188	**12.0**	303	**5.0**	421	**14.0**
45	**95.5**	189	**33.0**	304	**8.0**	422	**29.0**
46	**62.5**	190	**29.5**	305	**8.0**	423	**1.7**
47	**25.0**	195	**41.0**	306	**6.5**	424	**78.0**
50	**14.0**	196-1	**50.0**	307-1	**14.5**	425	**2.7**
51	**64.0**	196-2	**17.0**	307-2	**6.0**	426	**3.2**
52	**28.5**	197	**6.5**	308	**49.0**	427	**120**
54	**105**	198	**4.0**	309	**60.0**	428	**3.7**
55	**21.0**	199-1	**26.0**	310-1	**31.0**	429	**2.6**
55-1-1	**14.0**	199-2	**205**	310-2	**3.6**	430	**8.4**
55-1-2	**120**	200-1	**4.3**	311-1	**42.0**	431	**3.9**
55-2-1	**343**	200-2	**75.0**	311-2	**8.5**	432	**4.5**
57	**107**	201-1	**2.6**	312-1	**32.0**	433	**3.3**
58	**124**	201-2	**56.0**	312-2	**2.8**	434	**8.8**
59	**23.0**	202	**4.3**	313	**48.0**	435	**4.9**
61	**58.0**	203	**3.3**	314	**2.5**	436	**8.3**
64	**144**	204	**4.8**	315	**39.0**	437	**12.0**
65	**136**	205	**10.3**	316	**99.0**	438	**14.0**
68	**298**	206	**3.5**	317	**92.0**	439	**21.0**
69	**222**	207-1	**111**	318	**39.0**	440	**8.9**
70	**93.0**	207-2	**269**	319	**19.0**	441-1	**11.0**
71	**15.0**	208	**9.0**	319-1	**39.0**	441-2	**110**
72	**54.0**	209-1	**29.5**	319-2	**328**	442	**21.0**
73	**28.0**	209-2	**4.5**	320	**12.0**	443	**19.5**
74	**120**	210	**3.0**	321-1	**10.7**	444	**45.0**
75	**17.5**	211	**3.0**	321-2	**3.8**	445	**20.0**
76	**40.0**	212	**12.5**	322	**2.0**	446-1	**7.3**
77	**100**	213	**11.0**	323-1	**179**	446-2	**44.0**
78	**55.0**	214	**5.0**	323-2	**2.7**	447	**25.0**
79	**279**	215	**11.0**	324-1	**126**	448-1	**120**
80	**122**	216	**23.0**	324-2	**2.5**	448-2	**2.2**
81	**188**	217	**9.5**	325	**3.2**	449-1	**2.6**
83	**6.0**	218	**13.0**	326	**2.0**	449-2	**34.0**
84	**165**	219	**12.0**	327	**1.8**	450	**5.2**
86	**152**	220	**167**	328	**16.0**	451	**4.7**
88	**52.0**	221	**27.0**	329	**11.0**	452	**5.3**
89	**173**	222	**7.0**	330	**16.0**	453	**5.3**
90	**11.0**	223	**15.0**	331	**14.0**	454-1	**7.7**
91	**57.0**	224	**26.0**	332	**9.3**	454-2	**80.0**
92	**46.5**	225	**28.0**	333	**5.0**	455	**9.4**
93	**21.0**	226	**7,5**	334	**30.0**	456	**14.0**
94	**44.5**	227	**29.0**	335	**8.0**	457-1	**40.0**
95	**148**	228	**130**	336	**9.0**	457-2	**2.6**
97	**210**	229	**57.0**	337	**4.0**	458	**6.4**

100	**12.0**	230	**2.0**	338	**9.0**	459-1	**1.9**
101	**45.5**	231	**22.5**	339	**13.0**	459-2	**40.0**
102	**70.5**	232	**17.5**	340	**33.0**	460	**2.8**
103	**70.5**	233	**42.0**	341	**10.0**	461	**43.0**
106	**153**	234	**11.0**	342	**6.2**	462	**11.0**
107	**4.5**	235	**49.5**	343	**8.3**	463	**2.3**
108	**7.2**	236	**180**	344	**16.0**	464-1	**15.0**
109	**96.0**	237	**34.0**	345	**18.0**	464-2	**190**
110	**25.0**	238	**10.0**	346	**3.8**	465	**3.1**
111	**38.0**	238-1	**80.0**	347	**9.0**	466	**2.9**
112	**24.0**	238-2	**18.0**	348	**7.3**	467	**5.0**
113	**201**	239	**199**	349	**4.0**	467-1	**1.5**
114	**19.0**	240	**53.5**	350	**3.3**	467-2	**54.0**
115	**152**	241	**31.5**	351	**12.5**	468	**4.0**
116	**52.0**	242	**9.5**	352	**2.9**	468-1	**1.2**
117	**21.0**	243	**31.5**	353	**2.6**	469	**11.0**
119	**41.0**	244	**17.0**	354	**5.3**	470	**0.9**
120	**8.5**	244-1	**9.5**	355	**4.5**	471	**4.8**
121	**23.5**	244-2	**34.0**	356	**4.4**	472	**1.5**
122	**217**	245-1	**8.5**	357-1	**15.5**	473	**1.1**
123	**174**	245-2	**58.0**	357-2	**22.0**	474	**0.9**
124	**80.5**	246	**73.0**	358	**13.5**	475	**1.0**
125	**26.5**	247	**9.5**	359	**6.0**	476	**1.9**
126	**19.0**	248	**30.5**	360-1	**83.0**	477-1	**1.1**
127	**73.5**	249	**24.0**	360-2	**2693**	477-2	**27.0**
128	**37.0**	250	**17.0**	361	**5.2**	478	**1.1**
129	**11.0**	251	**106**	362	**4.6**	479	**2.1**
130	**62.0**	252	**109**	363	**6.2**	480	**1.5**
131	**15.5**	253	**39.0**	364	**5.1**	481	**1.9**
132	**6.0**	254	**48.0**	365	**8.5**	482	**2.4**
133	**30.0**	255	**86.0**	366-1	**1148**	483	**19.0**
134	**17.5**	256	**189**	366-2	**38.5**	484	**4.2**
135	**102**	257-1	**131**	367-1	**3.9**	485	**42.0**
136	**129**	257-2	**13.8**	367-2	**4.0**	486	**4.2**
137	**6.5**	258	**50.0**	368-1	**23.0**	487	**2.2**
138	**6.0**	259	**59.0**	368-2	**4.3**	488	**3.4**
139	**42.0**	260	**3.0**	369	**3.8**	489	**2.0**
140	**161**	261	**8.5**	370	**3.8**	490	**2.9**
141	**5.5**	262	**257**	371	**4.8**	491	**130**
142	**10.0**	263-1	**74.0**	372	**32.0**	492	**270**
143	**2.7**	263-2	**7.0**	373	**6.4**	493	**5.0**
144	**51.0**	264-1	**116**	374	**26.0**	494	**4.1**
145	**18.0**	264-2	**6.0**	375	**3.9**	495	**2.4**
146	**46.0**	265	**12.8**	376	**3.1**	496	**3.8**
147	**140**	266	**13.0**	377	**2.0**	497	**0.9**

148	**9.0**	267	**12.0**	378	**2.8**	498	**2.8**
149	**8.5**	268	**32.5**	379	**1.8**	499	**2.1**
150	**24.5**	269	**33.5**	380	**2.2**	500	**2.2**
151	**15.5**	270	**24.0**	382	**9.2**	501	**1.6**
152	**74.5**	271	**27.0**	383	**17.0**	502	**0.9**
153	**31.0**	272	**23.5**	384	**2.7**	503	**1.0**
154	**166**	273	**44.0**	385	**4.7**	504-1	**17.0**
155	**23.0**	274	**19.5**	386	**20.0**	504-2	**1.2**
156	**30.0**	275	**3.2**	387	**2.5**	505-1	**22.0**
158	**165**	276-1	**15.0**	388	**2.1**	505-2	**1.0**
159	**69.0**	276-2	**7.0**	389	**1.9**	506	**0.9**
160	**62.0**	277	**3.3**	390	**2.6**	507	**1.0**
161	**33.5**	278	**11.0**	391	**2.2**	508	**1.1**
162	**24.0**	279	**6.0**	392	**2.0**	509	**1.1**
163	**38.0**	280	**19.5**	393	**2.2**	510	**0.9**
163-1	**47.0**	280-1	**15.0**	394	**6.1**		
		280-2	**160**	394-1	**188**		

Experimental Example 2: Evaluation of Inhibitory Activity of Compounds Against Proliferation of Human Tumor Cells

This experiment assessed the inhibitory effect of the compounds against proliferation using in vitro cultured human leukemia cells MV-4-11 (carrying MLL-AF4), MOLM-13 (carrying MLL-AF9), and KG-1a (wild-type MLL, serving as a control cell line to exclude compounds exhibiting general cytotoxicity).

Reagents and Instruments:

Human acute lymphoblastic leukemia cells MV-4-11, purchased from American Type Culture Collection, Catalog Number: CRL-9591;

Human acute myeloid leukemia cells MOLM-13, purchased from COBIOER BIOSCIENCES CO., LTD, Catalog Number: CBP60678;

Human acute myeloid leukemia cells KG-1a, purchased from American Type Culture Collection, Catalog Number: CCL-246.1;

Inverted Microscope, purchased from Olympus Tokyo;

Countess™ Automated Cell Counter, purchased from Invitrogen, Model: C10281; and

Multilabel Reader, purchased from Bio-Tek, Model: Synergy HT.

Experimental method:

MV-4-11 cells were cultured in an IMDM medium containing 10% fetal bovine serum, KG-a cells were cultured in an IMDM medium containing 20% fetal bovine serum, or MOLM-13 cells were cultured in an RPMI-1640 medium containing 20% fetal bovine serum, each supplemented with 100 $U \cdot mL^{-1}$ penicillin and 100 $\mu g \cdot mL^{-1}$ streptomycin. These cells were cultured at 37°C with 5% CO_2. The suspensions of individual cell lines were prepared in their respective media and seeded into 96-well plates at a density of 4,000 cells/well for MV-4-11 and MOLM-13 cells, or 3,000 cells/well for KG-1a cells. On the day of the experiment, a compound stock solution was diluted in a 3-fold or 4-fold gradient using DMSO. Each gradient-diluted stock solution was then further diluted 250-fold with a complete medium to prepare a series of working solutions at different concentrations. Subsequently, 100 μL of working solution (containing a 2-fold concentration series of the test compound) was added to each well, with duplicate wells set up for each concentration.

Seven days after compound addition (on Day 7), an Alamar Blue assay reagent (MCE, HY-111391 / CS-0040317) was added to measure the fluorescence intensity in each well. Wells containing the cells in the growth medium supplemented with 0.1% DMSO (Day 7) served as high-read control wells. The readouts from the wells containing the cells in the growth medium supplemented with 0.1% DMSO on the day of compound addition (Day 0) served as low-reading control well. GraphPad Prism software was used to calculate the concentration required to inhibit 50% of cell proliferation (GI50), which serves as a cell proliferation inhibition activity index. The GI50 (half-maximal inhibitory concentration) of the compound was determined using the following nonlinear fitting formula: 4-Parameter Logistic Model or Sigmoidal Dose-Response Model:

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{(LogGI_{50} - X) \times Hill\ Slope}},$$

in which X indicates the logarithm of compound concentration, Y indicates an inhibition rate (% inhibition), Top indicates a readout of high-reading control well, and Bottom indicates a readout of low-reading control well, with

$$\text{Inhibition rate}(\%\ \text{inhibition}) = \frac{\text{Readout of Compound well} - \text{Readout of low-reading control well}}{\text{Readout of high-reading control well} - \text{Readout of low-reading control well}} \times 100\%.$$

Experimental results are shown in Table 2.

Table 2: Inhibitory Activity of Compounds Against Proliferation of Human Tumor Cells

Example	**MV-4-11 IC_{50} (nM)**	**MOLM-13 IC_{50} (nM)**	**KG-1a IC_{50} (nM)**	Example	**MV-4-11 IC_{50} (nM)**	**MOLM-13 IC_{50} (nM)**	**KG-1a IC_{50} (nM)**
15	23	ND	17000	**293**	2	24	20000
16	14	ND	20000	**294**	4.9	46	ND
17	17	ND	20000	**295**	19	47	ND
18-1	18	61	9700	**296-1**	0.75	3	ND
18-2	9.4	43	6500	**297-1**	12	36	ND
19	49	ND	20000	**305**	3.4	12	20000
20	54	ND	20000	**306**	2.8	7.7	20000
22-1	79	ND	20000	**307-2**	0.69	3.7	ND
22-2	22	ND	20000	**310-2**	0.97	6.2	ND
25-1	4.7	ND	12600	**311-2**	4.7	26	ND
42	3.3	26	3300	**312-2**	0.91	5.3	ND
282	5.4	25	ND	**314**	1.1	7.3	ND
55-1-1	18.5	44	ND	**321-1**	6.4	46	ND
72	57	ND	20000	**321-2**	2.6	17	ND
73	61	ND	20000	**323-2**	2.4	15	ND
75	25	78	20000	**324-2**	1.3	9.2	ND
83	5.5	33	7400	**342**	ND	5.3	ND
90	20	99	20000	**343**	ND	5.9	ND
91	68	ND	20000	**346**	ND	8.3	ND
100	17	51	ND	**349**	ND	16.5	ND
120	8.5	29.5	ND	**350**	ND	4.6	12000
121	42	128	ND	**351**	ND	44	>20000
128	56	30	ND	**352**	ND	6	ND
129	16	12	ND	**353**	4.1	5.4	>20000
131	50	40	ND	**354**	ND	5	ND
132	17	16	ND	**355**	ND	6.5	ND
133	49	31	ND	**356**	ND	4.1	ND
134	26	21	20000	**358**	ND	91	>20000
137	4.7	10	ND	**359**	ND	66	ND
138	3	7.6	20000	**361**	ND	3.3	ND
139	44	96	ND	**362**	ND	2.8	ND
141	1.1	5.4	ND	**363**	ND	20	ND
142	2.2	10	3600	**364**	ND	3.9	ND
145	13	29.5	19000	**365**	ND	14	ND
146	89	ND	ND	**368-2**	5	8.6	13000
148	0.95	3.6	ND	**369**	ND	3	ND
149	2.1	8.3	5300	**370**	ND	4.2	ND

150	21	36	ND	**371**	ND	5.3	>20000
151	40	61	ND	**373**	ND	6	ND
162	27	67	7000	**377**	ND	1.7	ND
164	2.2	6.1	ND	**378**	ND	5.8	ND
168	32	104	20000	**379**	0.4	2.5	11500
181-2	7.9	39	ND	**380**	ND	3.8	ND
182-2	ND	45	7500	**382**	ND	30	ND
183-2	7.9	39	11000	**384**	ND	4.1	ND
184-2	6.3	34	ND	**385**	ND	8.1	ND
185	26	70	20000	**387**	ND	8.9	ND
186-2	4.3	28	20000	**389**	ND	5.3	12000
187	15	36	ND	**391**	1.9	6	ND
188	9.1	27	ND	**393**	ND	16	ND
189	29	44	ND	**395**	ND	6.1	ND
190	25	40	ND	**396**	ND	22	>20000
195	13	35	ND	**398**	1.1	4.3	>20000
196-1	36	120	ND	**399-2**	ND	25	ND
196-2	9.6	28	ND	**400-2**	ND	12	ND
197	4	10.2	20000	**401-2**	ND	29	ND
200-1	3.2	10.2	20000	**402-2**	ND	65	11000
201-1	2.4	5.1	20000	**403-1**	ND	7.7	15000
202	1.8	11	20000	**403-2**	ND	38	ND
203	2.1	5.6	20000	**404**	ND	8.1	ND
204	2.8	11.2	18000	**405**	ND	7.2	ND
205	7.4	19	20000	**406**	ND	37	ND
206	3.5	15	20000	**408**	ND	4.2	ND
208	6.6	9.6	20000	**409**	ND	31	ND
209-1	12	21	ND	**410**	ND	37	ND
209-2	2	5	ND	**411**	ND	12	ND
210	7.1	41	ND	**412**	ND	39	ND
211	2.2	5.7	ND	**413**	ND	45	ND
212	16	31	ND	**416-2**	ND	69	ND
213	13	29	ND	**419**	ND	85	ND
214	7.5	12	ND	**420**	18	43	ND
215	6.7	13	ND	**423**	1.2	2.7	ND
216	22	32	ND	**425**	ND	9.9	ND
217	6.9	14	ND	**426**	ND	30	ND
218	6	11	ND	**428**	ND	52	ND
219	12	14	ND	**429**	ND	25	ND
221	12	27	ND	**430**	ND	46	ND
222	4.4	9	ND	**431**	4.7	15	ND
223	8.1	19	ND	**432**	ND	38	ND
224	14	36	ND	**433**	ND	18	ND
225	25	60	ND	**434**	ND	32	ND
226	2.1	5.3	ND	**435**	ND	26	ND

230	1	2.9	ND	**436**	ND	42	ND
231	6.1	16	ND	**440**	ND	56	ND
232	17	34	ND	**441-1**	ND	75	ND
234	5.8	14	ND	**445**	ND	68	ND
238-2	11	27	ND	**448-2**	ND	13	ND
242	5.9	28	ND	**449-1**	ND	6.1	ND
243	42	200	ND	**450**	ND	21	ND
244	13	64	ND	**451**	ND	25	ND
244-1	16	39	20000	**452**	ND	39	ND
244-2	54	130	ND	**453**	ND	22	ND
245-1	6.6	40	20000	**455**	ND	69	ND
247	9.2	22	ND	**457-2**	ND	5	ND
248	34	63	ND	**458**	ND	31	ND
249	50	44	ND	**459-1**	ND	4.7	ND
250	26	45	ND	**460**	ND	12	ND
257-2	17	31	20000	**463**	ND	4.3	ND
258	36	49	ND	**467-1**	ND	23	ND
259	55	110	ND	**468-1**	ND	19	ND
260	7.1	10	ND	**470**	ND	3.8	ND
261	9.6	23	20000	**472**	ND	24	ND
263-2	5.3	13	20000	**473**	ND	16	ND
264-2	4.7	12	20000	**474**	ND	11	ND
265	8.6	25	20000	**475**	ND	25	ND
266	13	33	ND	**477-1**	ND	10	ND
267	20	45	ND	**480**	ND	74	ND
268	36	96	ND	**481**	ND	5.5	ND
269	37	83	ND	**482**	ND	36	ND
271	12	33	ND	**488**	ND	19	ND
272	19	38	ND	**489**	ND	5.9	ND
275	2.6	9.4	20000	**495**	ND	27	ND
277	1.6	7.3	20000	**497**	ND	41	ND
278	8.3	24	ND	**498**	ND	23	ND
279	3.3	7.4	ND	**499**	ND	29	ND
280-1	6.9	27	ND	**502**	ND	9.8	ND
284-2	1.5	6.8	ND	**503**	ND	8.5	ND
285	5.4	23	ND	**504-2**	ND	13	ND
286	4.6	19	20000	**505-2**	ND	9.9	ND
287	9	48	20000	**506**	ND	13	ND
288	15	55	ND	**507**	ND	15	ND
289	11	45	20000	**508**	ND	11	ND
290	5.2	24	ND	**509**	ND	7.2	ND
291	1.6	7	ND	**510**	ND	9.9	ND
292	2.4	13	20000				

ND = Not detected

A compound exhibiting >100-fold selectivity toward control organelles compared to leukemia cells indicates lower cytotoxicity for that compound.

Experimental Example 3: Evaluation of Inhibitory Activity of Compounds Against MEIS1 Gene Expression in Human Tumor Cells

The effect of test samples on MEIS1 gene expression in vitro cultured human leukemia cells MV-4-11 (carrying MLL-AF4), MOLM-13 (carrying MLL-AF9), and OCI-AML3 (carrying NPM1c) was studied.

Reagents and Instruments:

Human acute lymphoblastic leukemia cells MV-4-11, purchased from American Type Culture Collection, Catalog Number: CRL-9591;

Human acute myeloid leukemia cells MOLM-13, purchased from COBIOER BIOSCIENCES CO., LTD, Catalog Number: CBP60678;

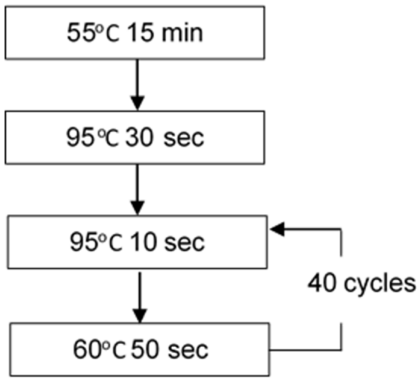
Human acute myeloid leukemia cells OCI-AML3, purchased from COBIOER BIOSCIENCES CO., LTD, Catalog Number: CBP60817;

MEIS1 Primer/Probe, purchased from IDT, Catalog Number: 40831613; and

GAPDH Primer/Probe, purchased from IDT, Catalog Number: 22214836.

Experimental method:

MV-4-11 cells were cultured in an IMDM medium containing 10% fetal bovine serum, or MOLM-13 and OCI-AML3 cells were cultured in an RPMI-1640 medium containing 20% fetal bovine serum, each supplemented with 100 $U \cdot mL^{-1}$ penicillin and 100 $\mu g \cdot mL^{-1}$ streptomycin. These cells were cultured at 37°C with 5% CO_2. The suspensions of individual cell lines were prepared in their respective media and seeded into 48-well plates at a density of 100,000 cells/well. On the day of the experiment, a compound stock solution was diluted in a 6-fold gradient using DMSO. Each gradient-diluted stock solution was then further diluted 250-fold with a complete medium to prepare a series of working solutions at different concentrations. Next, 250 µL of working solution (containing the complete medium with a 2-fold serial concentration of the test compound or a positive control compound, or containing a control complete medium) was added to each well. After 48 hours of incubation, cells from the 48-well plate were collected into 1 mL centrifuge tubes, centrifuged at 1000 rpm for 5 minutes, and the complete medium was removed. Cells were washed twice with 1 mL PBS and centrifuged to remove PBS. Total RNA was extracted using the RNeasy Mini Kit (250) (QIAGEN, 74106). The threshold cycle (Ct) value for gene expression was determined using the HiScript II U+ One Step qRT-PCR Probe Kit (Vazyme) (Vazyme, Q223-01), with 3 replicates per sample. The prepared reaction mixture was placed in an ABI 7500 real-time PCR instrument, and the reaction proceeded following the procedures below.



Next, for the relative MEIS1 gene expression, the concentration (EC50) that inhibits 50% of relative MEIS1 gene expression was calculated using GraphPad Prism 8 software. The EC_{50} (half-maximal inhibitory concentration) of the compound was determined using the following nonlinear fitting formula: 4-Parameter Logistic Model or Sigmoidal Dose-Response Model:

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{(LogEC_{50} - X) \times HillSlope}},$$

in which X indicates the logarithm of compound concentration, Y indicates a relative MEIS1 gene expression, Top and Bottom indicate highest and lowest readouts expressed as relative MEIS1 gene expression; and relative MEIS1 gene expression = $2^{-\Delta\Delta Ct}$, with ΔΔCt = threshold cycle Ct of MEIS1 gene - threshold cycle Ct of GAPDH.

Experimental results are shown in Table 3.

Table 3: Inhibitory Activity of Compounds Against MEIS1 Gene Expression in Human Tumor Cells

Example	**MV-4-11 MEIS1 EC_{50} (nM)**	**MOLM-13 MEIS1 EC_{50} (nM)**	**OCI-AML3 MEIS1 EC_{50} (nM)**	Example	**MV-4-11 MEIS1 EC_{50} (nM)**	**MOLM-13 MEIS1 EC_{50} (nM)**	**OCI-AML3 MEIS1 EC_{50} (nM)**
30	20	ND	ND	**305**	7.6	ND	ND

75	82	ND	ND	**306**	4.6	ND	ND
83	24	ND	ND	**310-2**	5.0	6.5	12
134	55	53	ND	**311-2**	19	11	23
137	16	9.0	ND	**312-2**	5.7	2.5	3.9
138	15	8.0	ND	**314**	13	3.4	8.9
142	6	2.3	ND	**321-1**	53	ND	ND
185	55	ND	ND	**321-2**	ND	10	32
186-2	3.8	ND	ND	**323-2**	8.6	8.4	17
188	42	ND	ND	**324-2**	7.3	1.3	9.5
189	89	ND	ND	**325**	7.6	4.2	ND
197	14	ND	ND	**326**	4.6	5.5	ND
200-1	12	1.0	13	**329**	63	17.9	ND
201-1	3.4	1.0	2.4	**331**	63	20.3	ND
202	3.5	ND	ND	**333**	15	6.2	ND
204	15	4.3	13	**336**	19	9.3	ND
205	18	ND	ND	**337**	13	5.5	ND
208	23	ND	ND	**338**	27	1.8	ND
257-2	19	15	33	**341**	26	6.0	ND
260	7.6	ND	ND	**346**	10	5.0	ND
261	8.5	ND	ND	**350**	6.8	4.0	ND
264-2	18	ND	ND	**352**	7.5	2.8	ND
265	54	38	70	**353**	7.4	2.4	21
275	8.3	7.7	16	**368-2**	7.8	9.1	17
277	6.5	3.3	12	**371**	3.0	1.1	ND
280-1	61	23	34	**379**	2.4	2.0	7.5
284-2	ND	5.9	5.8	**391**	2.9	2.1	11
292	15	ND	ND	**398**	1.9	2.6	13
293	23	9.1	31	**423**	1.3	2.3	6.1
297-1	32	12	34	**431**	5.5	4.6	33

ND = Not detected

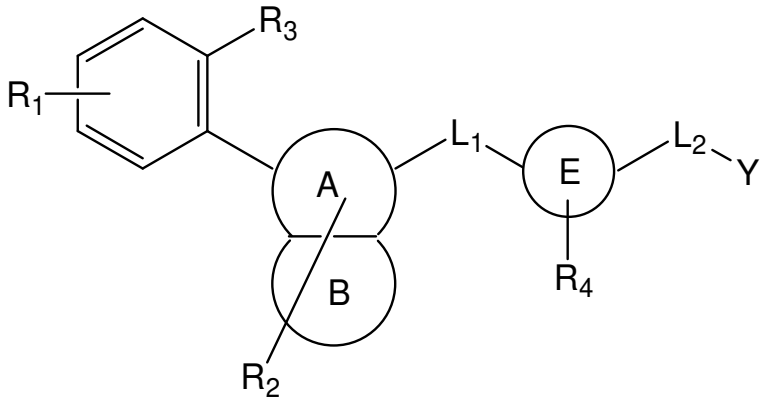
Described above provides only preferred embodiments of the present invention, which are not intended to limit the present invention. Any modification, equivalent substitution or the like made under the spirit and principle of the present invention shall be construed as falling within the protection scope of the present invention.

The foregoing embodiments and methods described in the present invention may vary depending on the ability, experience and preferences of those skilled in the art.

The method steps are listed only in a specific order in the present invention, without imposing any limits on the order of the method steps.

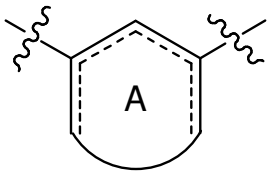
CLAIMS

1.A compound or a pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, wherein said compound has a structure of:



(I),

wherein



Ring A is , ------ represents a single or double bond, and said Ring A is a five- to seven-membered aromatic or heterocyclic ring;

Ring B is a five- to seven-membered nitrogenous heterocyclic ring;

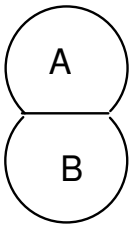
Ring E is a three- to eight-membered saturated or partially saturated aliphatic ring, an aromatic ring, or a four- to twelve-membered saturated or partially saturated heterocyclic ring;

L_1 and L_2 are independently selected from the group consisting of: a single bond, C_1-C_{10} alkylene, and -(C_0-C_{10} alkylene)-Q-(C_0-C_{10} alkylene)- , with Q selected from the group consisting of: -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{La})-, -N(R_{La})C(O)-, -N(R_{La})C(O)O-, -N(R_{La})C(O)N(R_{La})-, -N(R_{La})-, -S(O)$_2$-, -S(O)$_2$N(R_{La})-, -N(R_{La})S(O)$_2$-, -S(O)-, -S(O)N(R_{La})-, -N(R_{La})S(O)-, -C(=NR_{La})-, and -C(=NR_{La})-NR_{La}-; H atom(s) in said alkylene may be optionally substituted with a group selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4-10-membered heterocyclyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, hydroxyl, C_1-C_{10} alkoxy, halogenated C_1-C_{10} alkoxy, amino, and C_1-C_{10} alkylamino; H in said cycloalkyl, aryl or heterocyclyl may be optionally substituted with a group selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, and halogenated C_1-C_{10} alkyl; R_{La} is selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl;

R_1 is one or more independent substituents on the benzene ring, and each R_1 is independently selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{101}, -C(O)R_{101}, -C(O)OR_{101}, -NR_{102}C(O)OR_{101}, -OC(O)R_{101}, -NR_{102}S$O_2$$R_{101}$, -S$O_2NR_{101}$$R_{102}$, -N$R_{102}$C(O)$R_{101}$, -C(O)N$R_{101}$$R_{102}$, -N$R_{101}$$R_{102}$, -S$R_{101}$, -S(O)$R_{101}$, -S$(O)_2$$R_{101}$, -$SO_3$H, -N$R_{102}$($CR_{103}R_{104}$)$_tOR_{101}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with t being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR'', -NR'SO_2R'', -SO_2NR'R'', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_{101} to R_{104} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-

10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;



R_2 is one or more independent substituents on the Ring , and each R_2 is independently selected from the group consisting of: H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{201}, -C(O)R_{201}, -C(O)OR_{201}, -NR_{202}C(O)OR_{201}, -$OC(O)R_{201}$, -$NR_{202}SO_2R_{201}$, -$SO_2NR_{201}R_{202}$, -$NR_{202}C(O)R_{201}$, -$C(O)NR_{201}R_{202}$, -$NR_{201}R_{202}$, -SR_{201}, -$S(O)R_{201}$, -$S(O)_2R_{201}$, -SO_3H, -$NR_{202}(CR_{203}R_{204})_jOR_{201}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with j being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_{201} to R_{204} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_3 is selected from the group consisting of: H, halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{301}, -C(O)R_{301}, -C(O)OR_{301}, -NR_{302}C(O)OR_{301}, -$OC(O)R_{301}$, -$NR_{302}SO_2R_{301}$, -$SO_2NR_{301}R_{302}$, -$NR_{302}C(O)R_{301}$, -$C(O)NR_{301}R_{302}$, -$NR_{301}R_{302}$, -SR_{301}, -$S(O)R_{301}$, -$S(O)_2R_{301}$, -SO_3H, -$NR_{302}(CR_{303}R_{304})_iOR_{301}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with i being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_{301} to R_{304} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

or, R_{301} and R_{302}, together with the atom attached thereto, form heterocyclyl, and said heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-

C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_5, -$C(O)R_5$, -$C(O)OR_5$, -$NR_6C(O)OR_5$, -$OC(O)R_5$, -$NR_6SO_2R_5$, -$SO_2NR_5R_6$, -$NR_6C(O)R_5$, -$C(O)NR_5R_6$, -NR_5R_6, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -SO_3H, -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl); wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_5 and R_6 are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R_4 is one or more independent substituents on the Ring E, and each R_4 is independently selected from the group consisting of: H, halogen, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_{401}, -$C(O)R_{401}$, -$C(O)OR_{401}$, -$NR_{102}C(O)OR_{401}$, -$OC(O)R_{401}$, -$NR_{402}SO_2R_{401}$, -$SO_2NR_{401}R_{402}$, -$NR_{402}C(O)R_{401}$, -$C(O)NR_{401}R_{402}$, -$NR_{401}R_{402}$, -SR_{401}, -$S(O)R_{401}$, -$S(O)_2R_{401}$, -SO_3H, -$NR_{402}(CR_{403}R_{404})_mOR_{104}$, -($C_0$-$C_6$ alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), with m being an integer ranging from 0 to 5; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

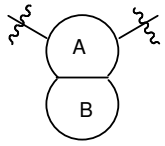
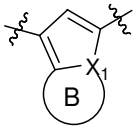
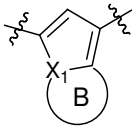
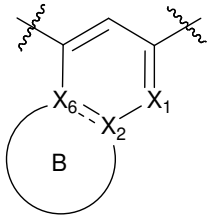
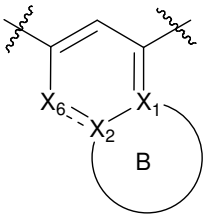
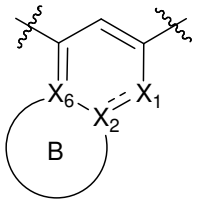
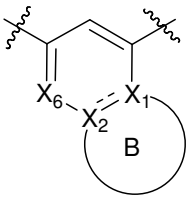
R_{401} to R_{404} are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

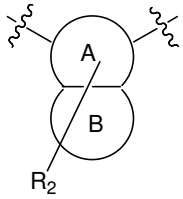
Y is selected from the group consisting of: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, three- to eight-membered saturated or partially saturated alcyl, aryl, four- to twelve-membered heterocyclyl, aryl-fused three- to eight-membered alcyl, aryl-fused three- to eight-membered heterocyclyl, three- to eight-membered aliphatic ring-fused aryl, three- to eight-membered aliphatic ring-fused heterocyclyl, three- to eight-membered heterocyclic ring-fused three- to eight-membered aliphatic ring, three- to eight-membered heterocyclic ring-fused aryl, and three- to eight-membered heterocyclic ring-fused five- to ten-membered heterocyclyl, and Y may be optionally substituted with one or more R^Y groups, with R^Y selected from the group consisting of: H, =O, , C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, -OR_7, -$C(O)R_7$, -$C(O)OR_7$, -$NR_8C(O)OR_7$, -$OC(O)R_7$, -$NR_8SO_2R_7$, -$SO_2NR_7R_8$, -$NR_7C(O)R_8$, -$C(O)NR_7R_8$, -NR_7R_8, -SR_7, -$S(O)R_7$, -$S(O)_2R_7$, -SO_3H, -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -SO_2-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -S-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -O-(C_0-C_6 alkylene)-(C_6-C_{10} aryl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl); wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be

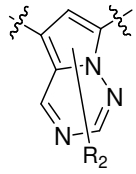
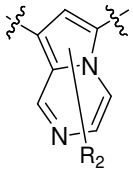
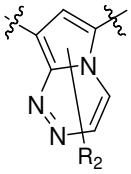
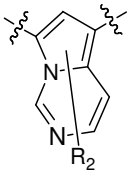
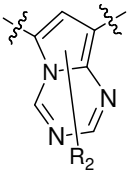
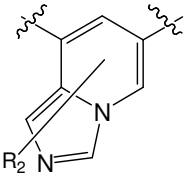
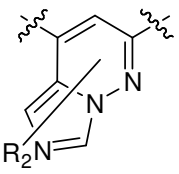
optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

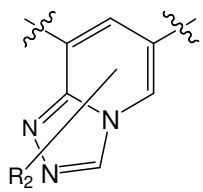
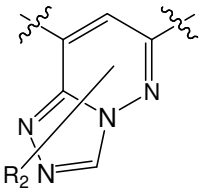
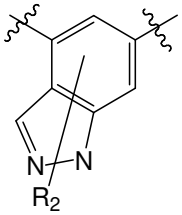
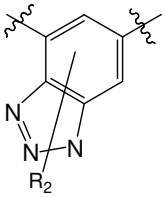
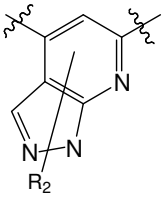
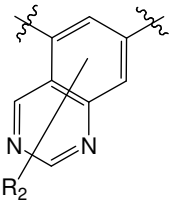
R_7 and R_8 are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl; wherein said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR", -NR'SO_2R", -SO_2NR'R", -NR'C(O)R", -C(O)NR'R", -NR'R", -SR', -SOR', -SO_2R', -SO_3H, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, C_1-C_{10} cyanoalkyl, C_3-C_{10} cycloalkyl, phenyl, and 4-10-membered heterocyclyl; and

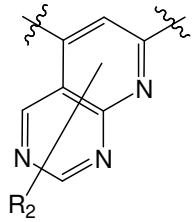
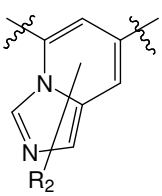
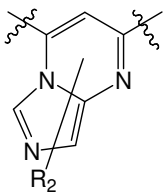
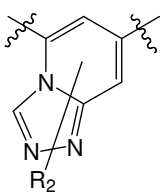
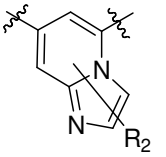
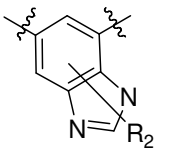
R' and R" are each independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{12} aralkyl, 4-10-membered heterocyclyl, and 4-10-membered heterocyclylalkyl.

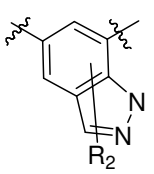
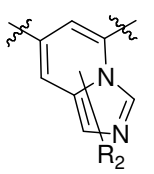
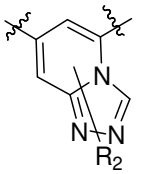
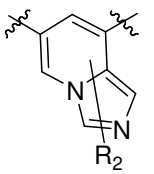
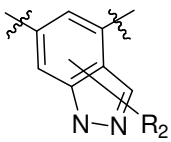
2.The compound according to claim 1, wherein said  moiety is  ,  ,  ,  ,  , or  , wherein X_1 is N or C, X_2 is N or C, X_6 is N or C, and ------ represents a single or double bond;

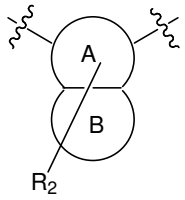
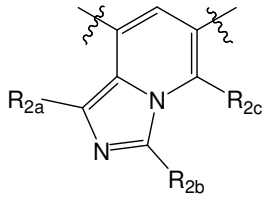
preferably, said  moiety is selected from the following structures:

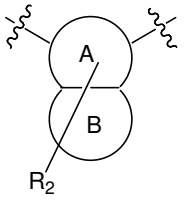
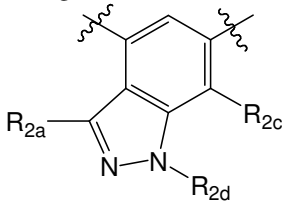
 ,  ,  ,  ,  ,  ,  ,

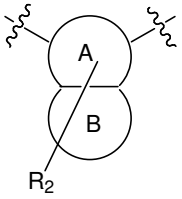
 ,  ,  ,  ,  ,  ,

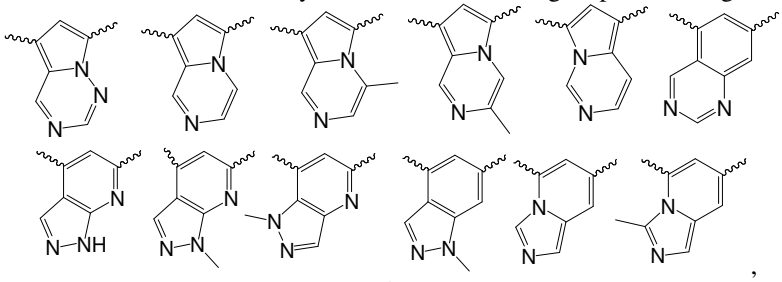
 ,  ,  ,  ,  ,  ,






, , , , and ;

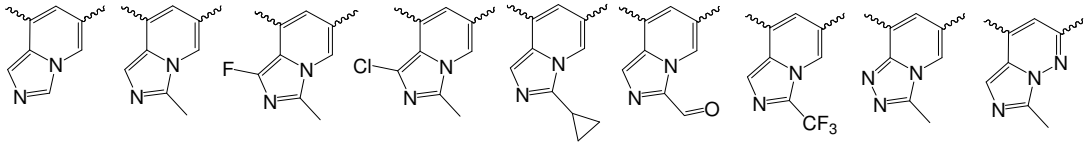


preferably, said moiety is , wherein R_{2a} is selected from the group consisting of: H and halogen, R_{2b} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), and -C(O)(C_0-C_6 alkyl), and R_{2c} is selected from the group consisting of: H and halogen;

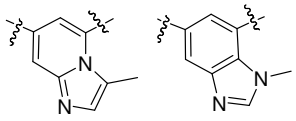


preferably, said moiety is , wherein R_{2a} is selected from the group consisting of: H and halogen, R_{2d} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), and -C(O)(C_0-C_6 alkyl), and R_{2c} is selected from the group consisting of: H and halogen; and


more preferably, said moiety is selected from the group consisting of:


,

,


, and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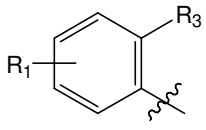
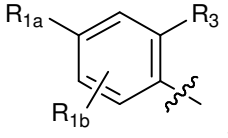
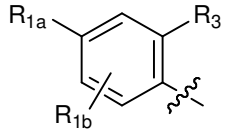
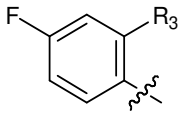
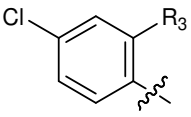
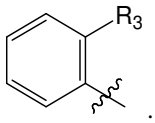
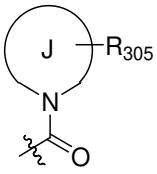
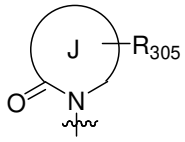
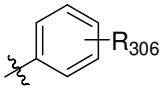


3.The compound according to claim 1 or 2, wherein said moiety is , wherein R_{1a} is H or halogen;

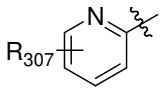
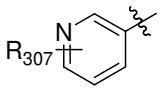
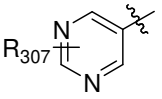
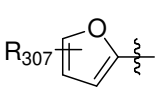
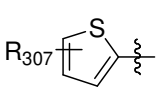
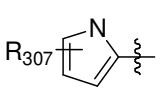
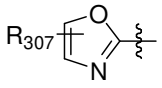
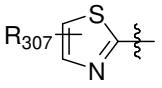
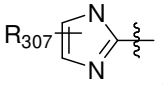
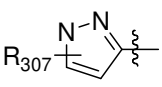
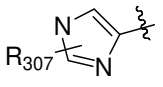
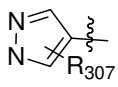
R_{1b} is one or more independent substituents on a benzene ring, each of which is independently selected from

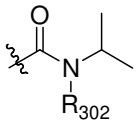
the group consisting of: H, halogen, C_1-C_6 alkyl, halogen, cyano, nitro, azido, halogenated C_1-C_6 alkyl, -N(C_0-C_6 alkyl)C(O)(C_0-C_6 alkyl), and -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl);
preferably, R_{1a} is H, F, or Cl;
more preferably, said  moiety is  ,  or  .

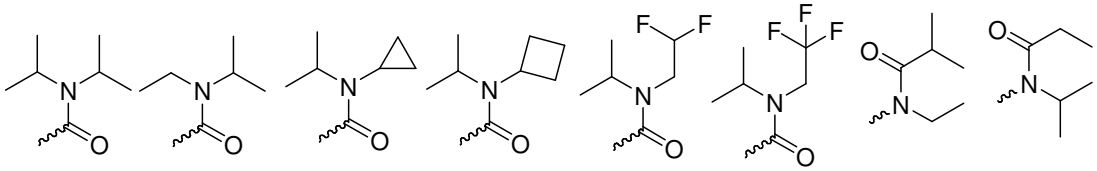
4.The compound according to any one of claims 1 to 3, wherein R_3 is -$NR_{302}C(O)R_{301}$ or -$C(O)NR_{301}R_{302}$, wherein R_{301} or R_{302} is independently selected from the group consisting of: H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_3-C_{10} cycloalkylalkyl, optionally substituted 4-10-membered heterocyclyl, and optionally substituted 4-10-membered heterocyclylalkyl; or,

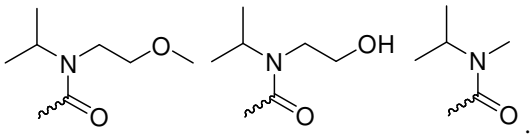
R_3 is  or  , wherein Ring J is a 4-8-membered saturated heterocyclic ring, and R_{305} is one or more independent substituents on Ring J, each of which is independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl; or,

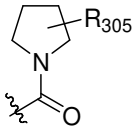
R_3 is -(C_0-C_6 alkylene)-(C_6-C_{10} aryl), preferably  , wherein R_{306} is one or more independent substituents on a benzene ring, each of which is independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl; or,

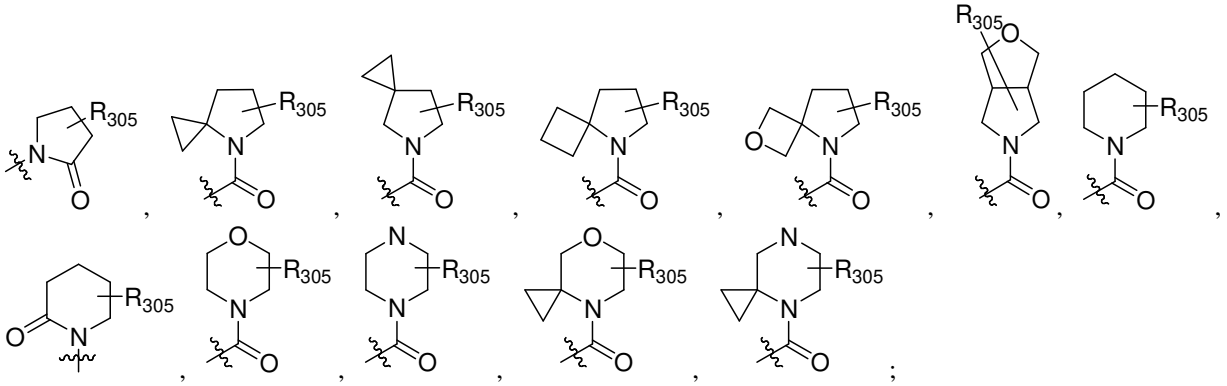
R_3 is -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), preferably selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein R_{307} is one or more independent substituents on a ring, each of which is independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, hydroxyl, amino, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, and 4-10-membered heterocyclyl.

5.The compound according to claim 4, wherein R_3 is  ;
preferably, R_{302} is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; and
more preferably, R_3 is selected from the group consisting of:

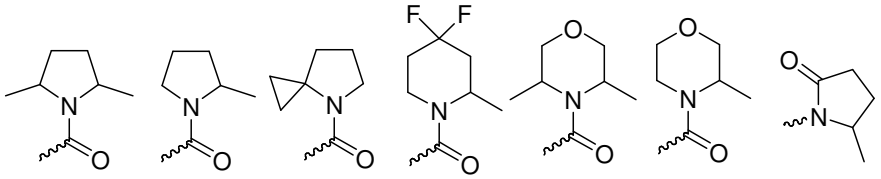


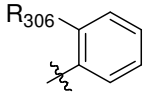
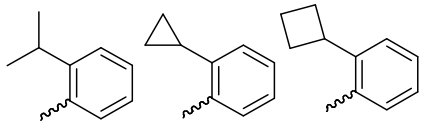


6.The compound according to claim 4, wherein R_3 is selected from the group consisting of:  ,

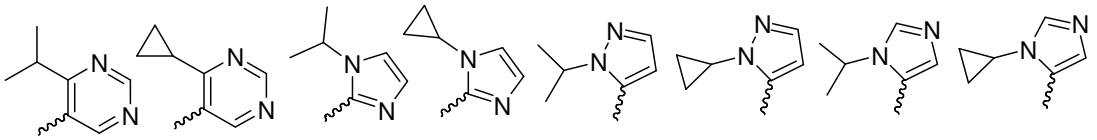


preferably, R_{305} is selected from the group consisting of: H, halogen, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and 4-6-membered heterocycloalkyl; and
more preferably, R_3 is selected from the group consisting of:

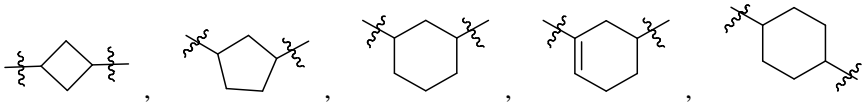
 .

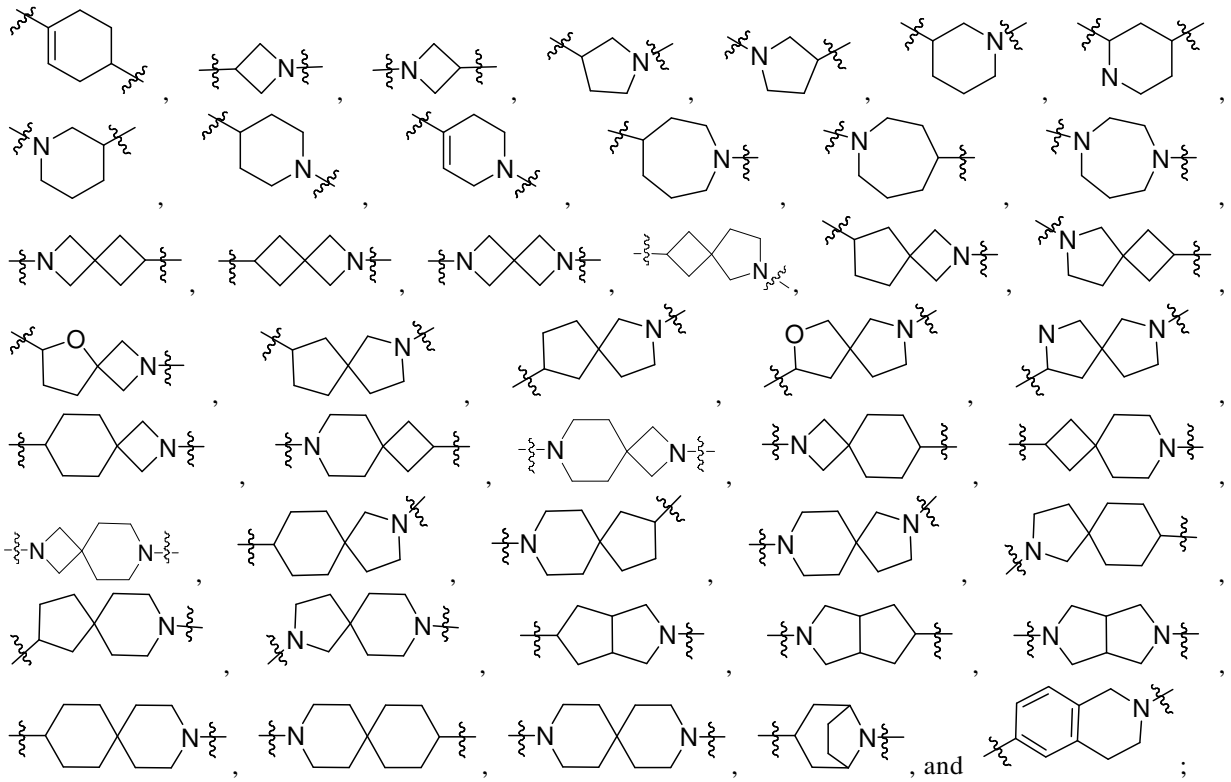
7.The compound according to claim 4, wherein R_3 is  ;
preferably, R_{306} is selected from the group consisting of: H, halogen, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; and
more preferably, R_3 is selected from the group consisting of:  .

8.The compound according to claim 4, wherein R_{307} is selected from the group consisting of: H, halogen, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; and
preferably, R_3 is selected from the group consisting of:

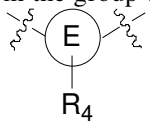
 .

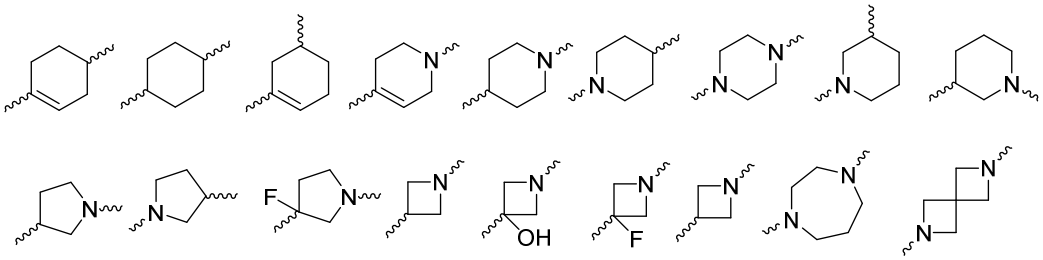
9.The compound according to any one of claims 1 to 8, wherein L_1 is a single bond, C_1-C_6 alkylene, -O-, -S- or -N(R_{La})-, and R_{La} is selected from the group consisting of: H and C_1-C_6 alkyl, preferably a single bond.

10.The compound according to any one of claims 1 to 9, wherein said moiety is selected from the group consisting of:  ,

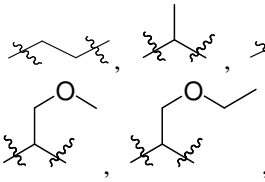
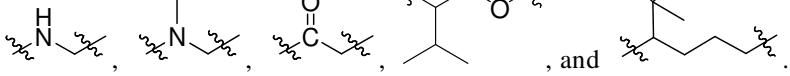
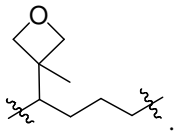

, and ;

preferably, R_4 is selected from the group consisting of: H, halogen, =O, cyano, nitro, azido, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, and C_1-C_6 cyanoalkyl, more preferably selected from the group consisting of: H, halogen, hydroxyl, C_1-C_3 alkyl, and C_1-C_3 alkoxy; and

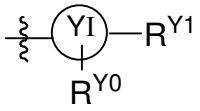
more preferably, said  moiety is selected from the group consisting of:


.

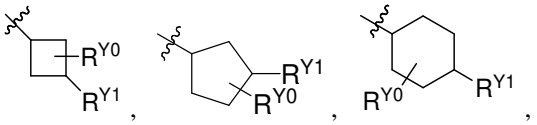
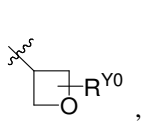
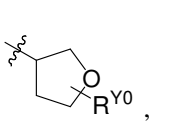
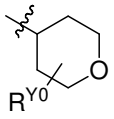
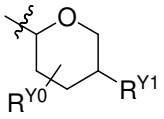
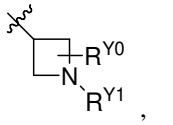
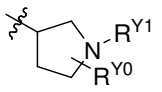
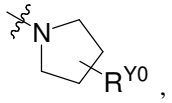
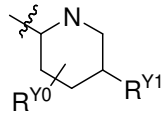
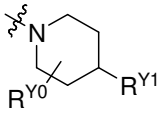
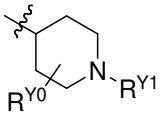
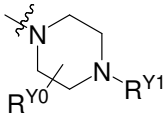
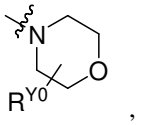
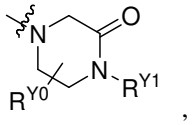
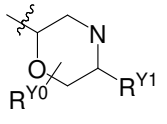
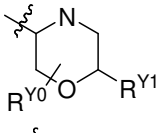
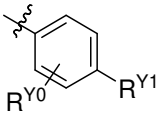
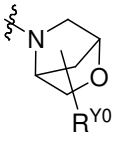
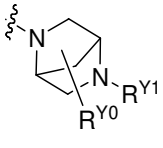
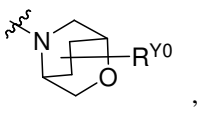
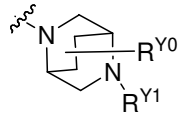
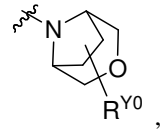
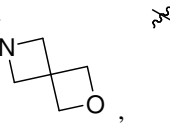
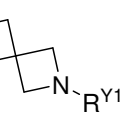
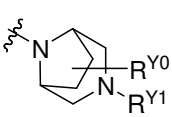
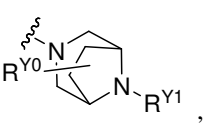
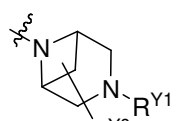
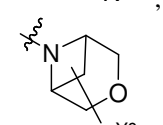
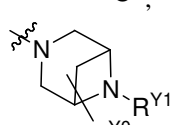
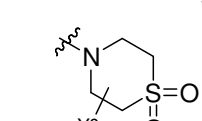
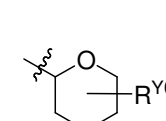
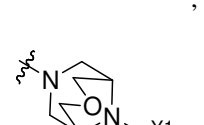
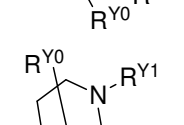
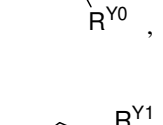
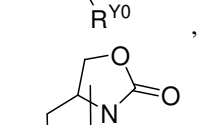
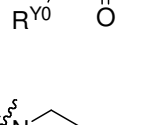
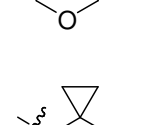
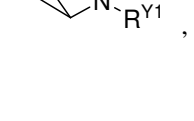
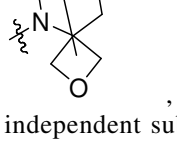
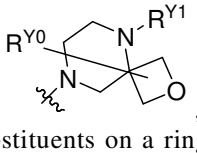
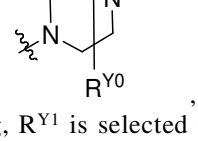
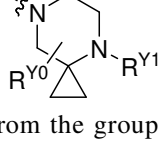
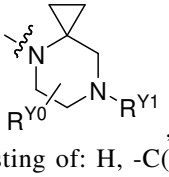
11.The compound according to any one of claims 1 to 10, wherein L_2 is a single bond, C_1-C_6 alkylene or -(C_0-C_6 alkylene)-Q-(C_0-C_6 alkylene)-, with Q selected from the group consisting of: -O-, -C(O)-, -N(C_0-C_3 alkyl)-, and -N(C_0-C_3 alkyl)C(O)-, wherein H atom(s) in said alkylene may be optionally substituted with a group selected from the group consisting of: H, C_1-C_3 alkyl, halogen, cyano, halogenated C_1-C_3 alkyl, hydroxyl, C_1-C_3 alkoxy, halogenated C_1-C_3 alkoxy, amino, and C_1-C_6 alkylamino; and

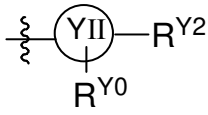
preferably, L_2 is selected from the group consisting of: methylene,  , -O-, -C(O)-, -NHC(O)-,  , and  .

12.The compound according to any one of claims 1 to 11, wherein Y is selected from groups in sets Y1, Y2, Y3, Y4, and Y5;



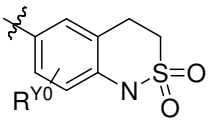
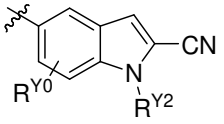
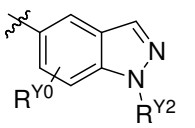
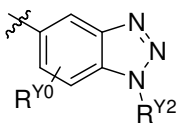
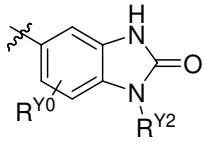
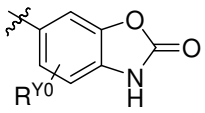
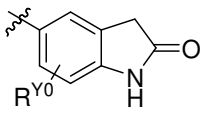
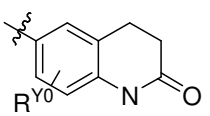
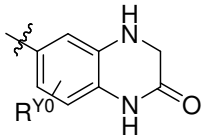
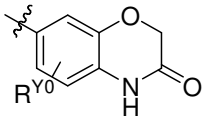
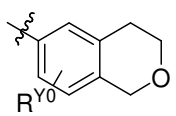
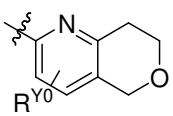
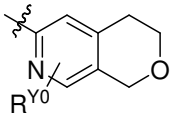
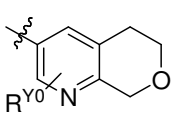
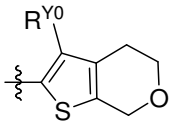
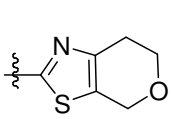
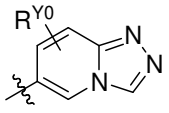
Y1 is , wherein Ring YI is a 3-8-membered saturated or partially saturated aliphatic ring, a benzene ring, or a 4-12-membered saturated or partially saturated heterocyclic ring;

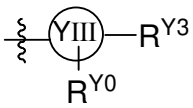
preferably, Y1 is selected from the group consisting of:  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and , R^{Y0} is one or more independent substituents on a ring, R^{Y1} is selected from the group consisting of: H, -C(O)R_7, -C(O)OR_7, -NR_8SO_2R_7, -NR_8C(O)OR_7, -NR_8C(O)R_7, -C(O)NR_7R_8, -NR_7R_8, -S$(O)_2R_7$, C_1-C_6 alkyl, -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), and -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl); wherein said C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl; R_7 and R_8 are each independently selected from the group consisting of: H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), and -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl); wherein said C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

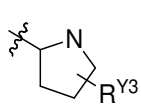
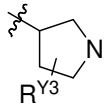
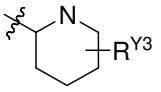
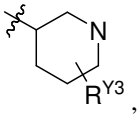
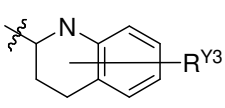
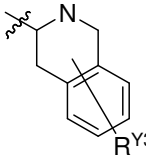
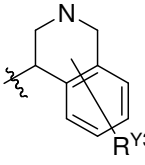
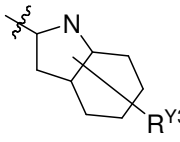
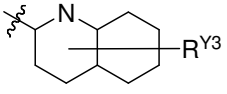
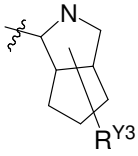
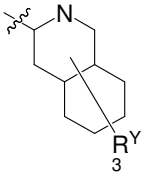
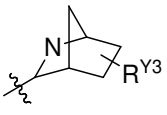
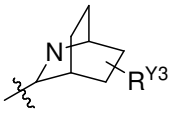
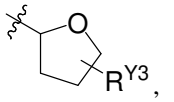
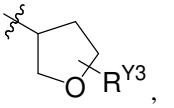
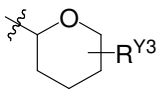
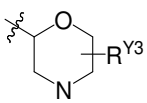
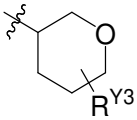


Y2 is , wherein Ring YII is a benzene ring-fused four- to eight-membered aliphatic ring,

a benzene ring-fused four- to eight-membered heterocyclic ring, or a bicyclic heterocyclic ring;

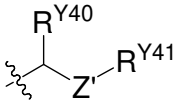
preferably, Y2 is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , R^{Y0} is one or more independent substituents on a ring, R^{Y2} is selected from the group consisting of: H, cyano, C_1-C_6 alkyl, and 4-10-membered heterocyclyl, wherein said C_1-C_6 alkyl or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: =O, halogen, cyano, nitro, amino, 4-10-membered heterocyclyl, C_3-C_8 cycloalkyl, 4-10-membered heterocyclyl, -(C_0-C_4 alkylene)-OH, -(C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy, -C(O)O(C_0-C_6 alkyl), -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl), -N(C_0-C_6 alkyl)C(O) (C_0-C_6 alkyl), -SO_2(C_0-C_6 alkyl), -SO_2(phenyl), -SO_2(halogenated C_1-C_6 alkyl), -SO_2N(C_0-C_6 alkyl)(C_0-C_6 alkyl), -SO_2NH(phenyl), -NHSO_2(C_0-C_6 alkyl), -NHSO_2(phenyl) and -NHSO_2(halogenated C_1-C_6 alkyl);

Y3 is  , wherein Ring YIII is a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring, a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring-fused benzene ring, a four- to eight-membered monocyclic nitrogenous saturated heterocyclic ring-fused four- to eight-membered aliphatic ring, or a six- to ten-membered bridged nitrogenous saturated heterocyclic ring;

preferably, Y3 is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , R^{Y3} is one or more independent substituents on a ring, and R^{Y3} is selected from the group consisting of: H, =O, , C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy,

halogenated C_1-C_6 alkoxy, -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl); wherein said C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

R^{Y0} is selected from the group consisting of: H, =O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, cyano, nitro, azido, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, -OR_7, -$C(O)R_7$, -$C(O)OR_7$, -$NR_8C(O)OR_7$, -$OC(O)R_7$, -$NR_8SO_2R_7$, -$SO_2NR_7R_8$, -$NR_7C(O)R_8$, -$C(O)NR_7R_8$, -NR_7R_8, -SR_7, -$S(O)R_7$, -$S(O)_2R_7$, -SO_3H, -(C_0-C_6 alkylene)-(phenyl), -SO_2-(C_0-C_6 alkylene)-(phenyl), -S-(C_0-C_6 alkylene)-(phenyl), -O-(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -SO_2-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -S-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -O-(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), -(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -SO_2-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), -S-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), and -O-(C_0-C_6 alkylene)-(C_3-C_6 cycloalkyl), and said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, -OR', -C(O)R', -C(O)OR', -NR'C(O)R'', -C(O)NR'R'', -NR'R'', C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, halogenated C_1-C_6 alkoxy, C_1-C_6 cyanoalkyl, C_3-C_6 cycloalkyl, phenyl, and 4-10-membered heterocyclyl;

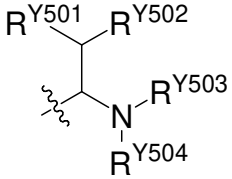
Y4 is 

, wherein,

R^{Y40} is selected from the group consisting of: C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, and C_1-C_3 alkyl-substituted 3-6-membered heterocyclyl;

Z' is selected from the group consisting of: C_0-C_6 alkylene, -(C_0-C_3 alkylene)-O-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-S-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-C(O)NH-(C_0-C_3 alkylene)-, -(C_0-C_3 alkylene)-NHC(O)-(C_0-C_3 alkylene)-, and C_3-C_6 cycloalkylene; wherein H in said alkylene is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, and amino;

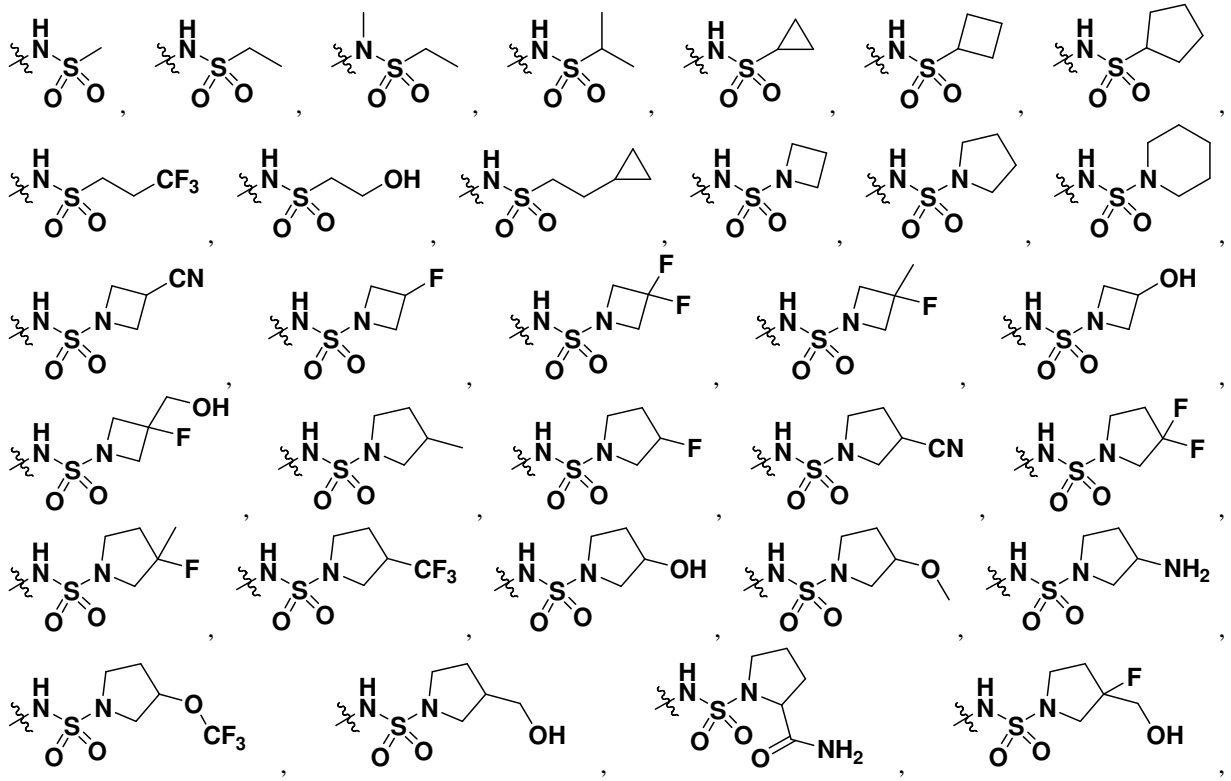
R^{Y41} is selected from the group consisting of: H, halogen, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 4-12-membered heterocyclyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl); wherein H in said alkyl, cycloalkyl, aryl, or heterocyclyl is optionally substituted with a group selected from the group consisting of: halogen, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 4-12-membered heterocyclyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)CO(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)CON(4-10-membered heterocyclyl), -N($C_{0\text{-}10}$ alkyl)SO_2(4-10-membered heterocyclyl), -O(4-10-membered heterocyclyl), -S(4-10-membered heterocyclyl), -SO(4-10-membered heterocyclyl), -SO_2(4-10-membered heterocyclyl), -SO_2N($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), -COO(4-10-membered heterocyclyl), -OCO(4-10-membered heterocyclyl), -CON($C_{0\text{-}10}$ alkyl)(4-10-membered heterocyclyl), and -CO(4-10-membered heterocyclyl), wherein H in said alkyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6hydroxylalkyl, C_1-C_6 alkoxyalkyl, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl);

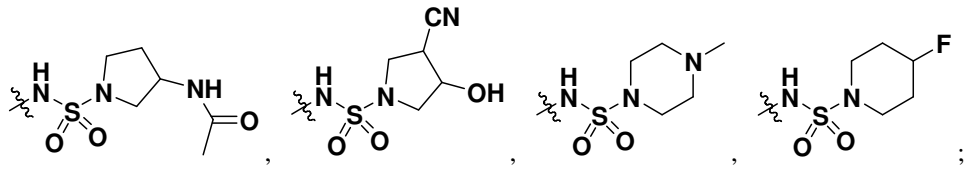
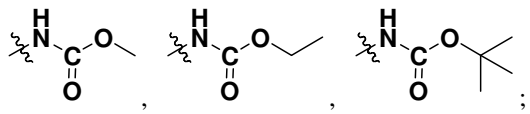
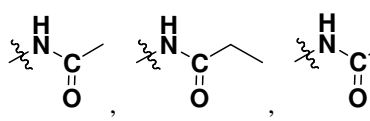
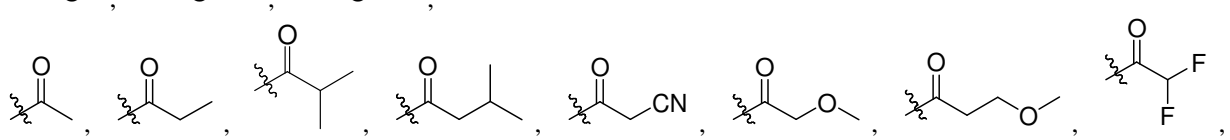
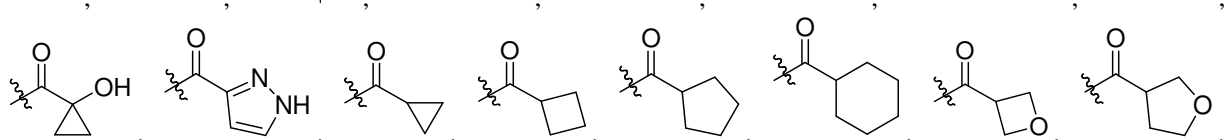
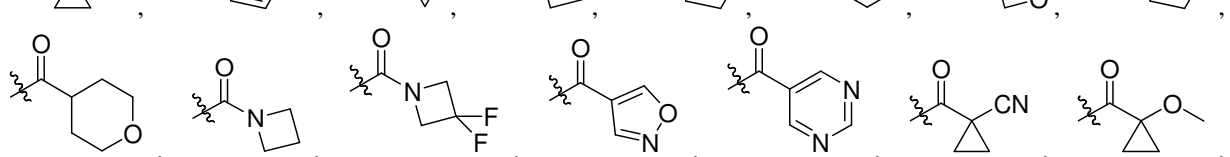
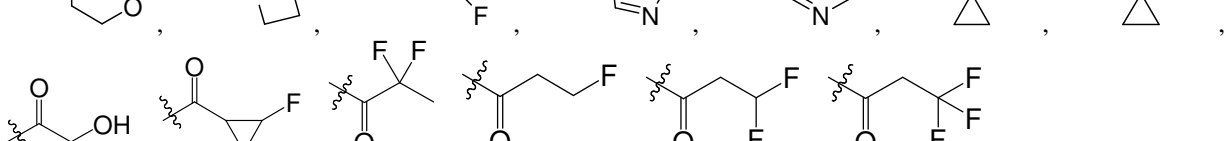
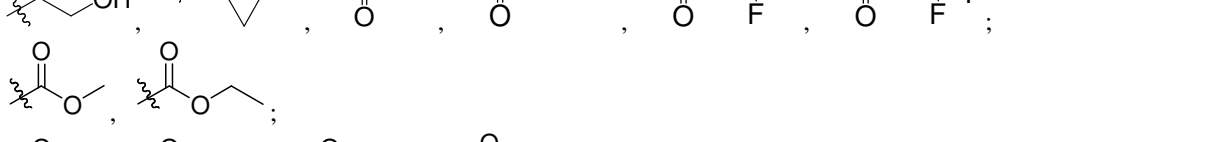
Y5 is 

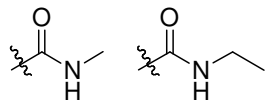
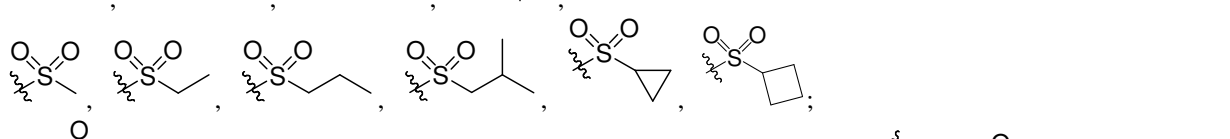
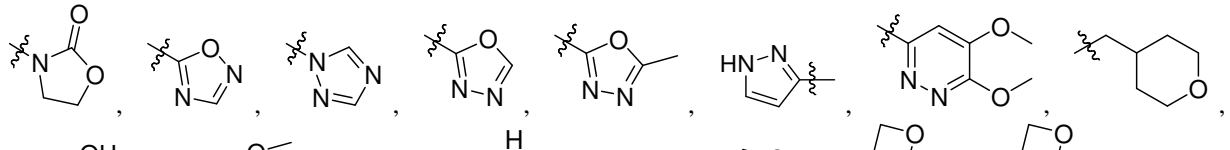
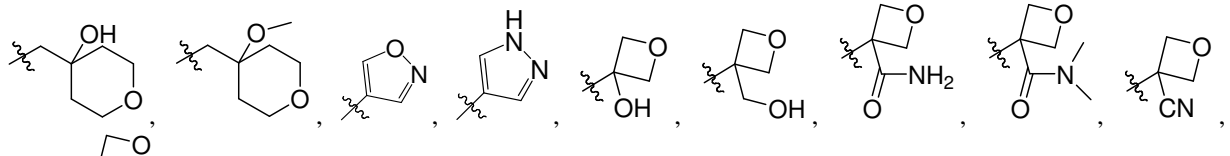
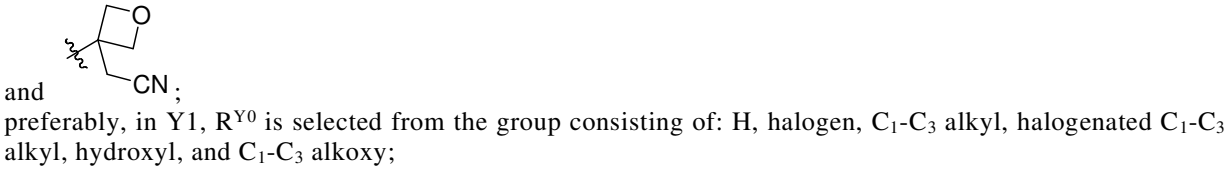
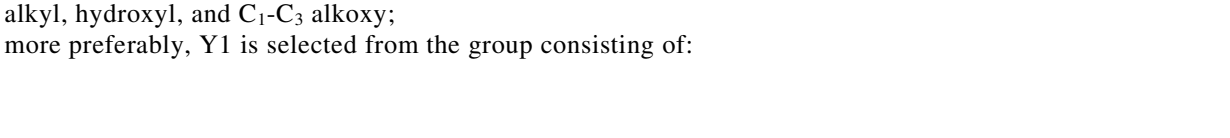
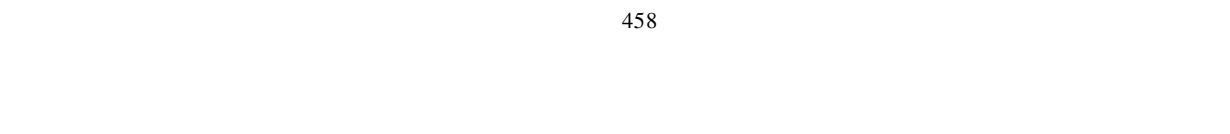
, wherein R^{Y501} and R^{Y502} are independently selected from the group consisting of: H, halogen, hydroxyl, amino, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, and -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), wherein said alkyl or cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y501} and

R^{Y502}, together with the carbon atom attached thereto, form an aliphatic ring or a heterocyclic ring, wherein said aliphatic ring or heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkyl, and halogenated C_1-C_6 alkyl;
R^{Y503} and R^{Y504} are independently selected from the group consisting of: H and C_1-C_6 alkyl, wherein said alkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_6 alkoxy, and C_1-C_6 alkylamino; or, R^{Y503} and R^{Y504}, together with the nitrogen atom attached thereto, form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -CO($C_{0\text{-}10}$ alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in said $C_{0\text{-}10}$ alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -S($C_{0\text{-}10}$ alkyl), -SO($C_{0\text{-}10}$ alkyl), -SO_2($C_{0\text{-}10}$ alkyl), -SO_2N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), and -CO($C_{0\text{-}10}$ alkyl).

13.The compound according to claim 12, wherein R^{Y1} is selected from the group consisting of: -$NR_8SO_2R_7$, -$NR_8C(O)OR_7$, -$C(O)R_7$, -$C(O)OR_7$, -$C(O)NR_7R_8$, -$S(O)_2R_7$, and -$(CH_2)_n$(4-10-membered heterocyclyl),
R_7 is selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, -(C_0-C_3 alkylene)-(C_3-C_6 cycloalkyl), and -(C_0-C_3 alkylene)-(4-10-membered heterocyclyl), wherein said C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4-10-membered heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkoxy, hydroxyl-substituted C_1-C_6 alkyl, -C(O)N(C_0-C_6 alkyl)(C_0-C_6 alkyl), and -N(C_0-C_6 alkyl)C(O)(C_0-C_6 alkyl),
R_8 is selected from the group consisting of: H and C_1-C_6 alkyl;
more preferably, R^{Y1} is selected from the group consisting of:
H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, hydroxyl-substituted C_1-C_6 alkyl, C_1-C_6 alkoxyalkyl, -O-(hydroxyl-substituted C_1-C_6 alkyl), -O-(C_1-C_6 alkoxyalkyl), C_1-C_6 cyanoalkyl,



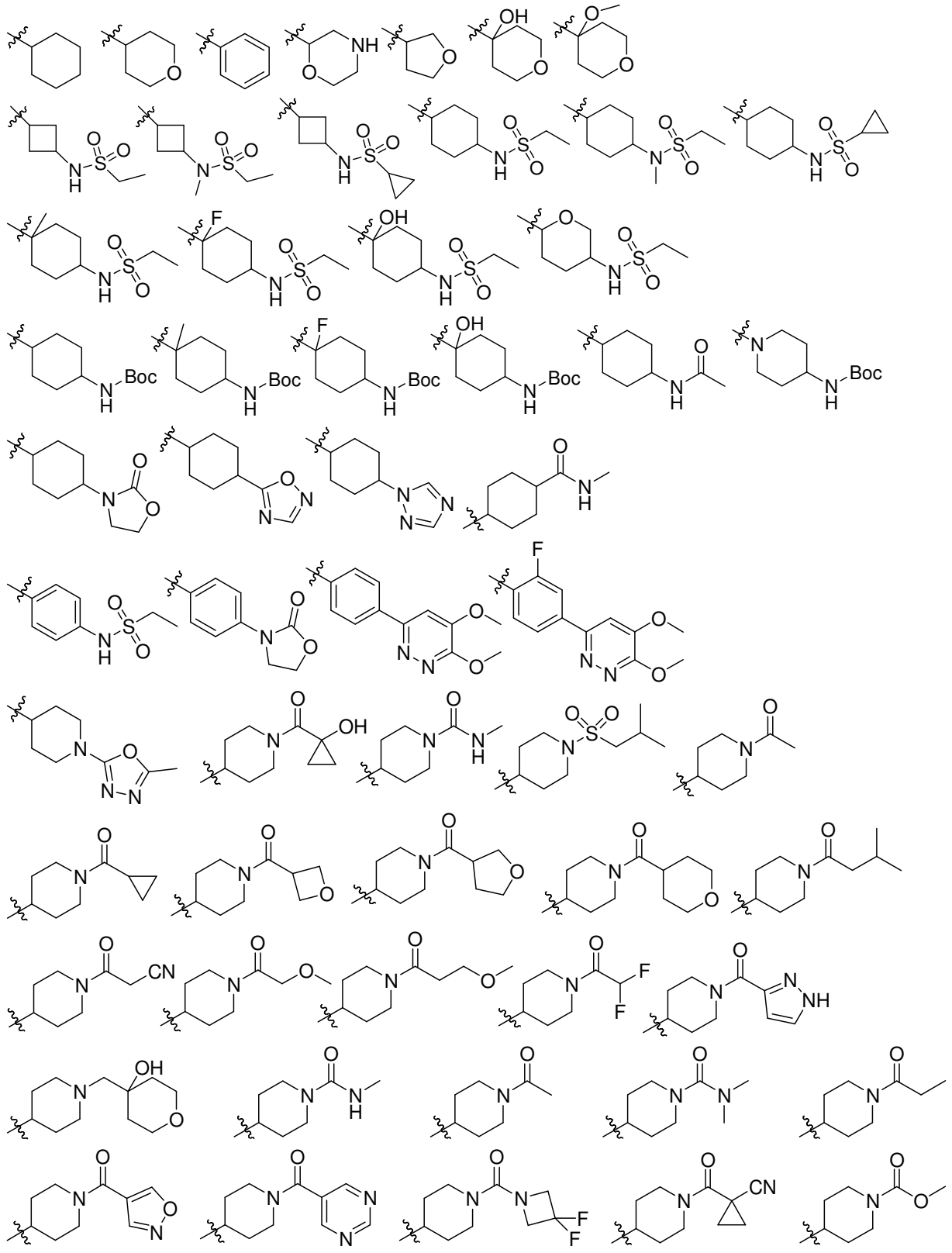









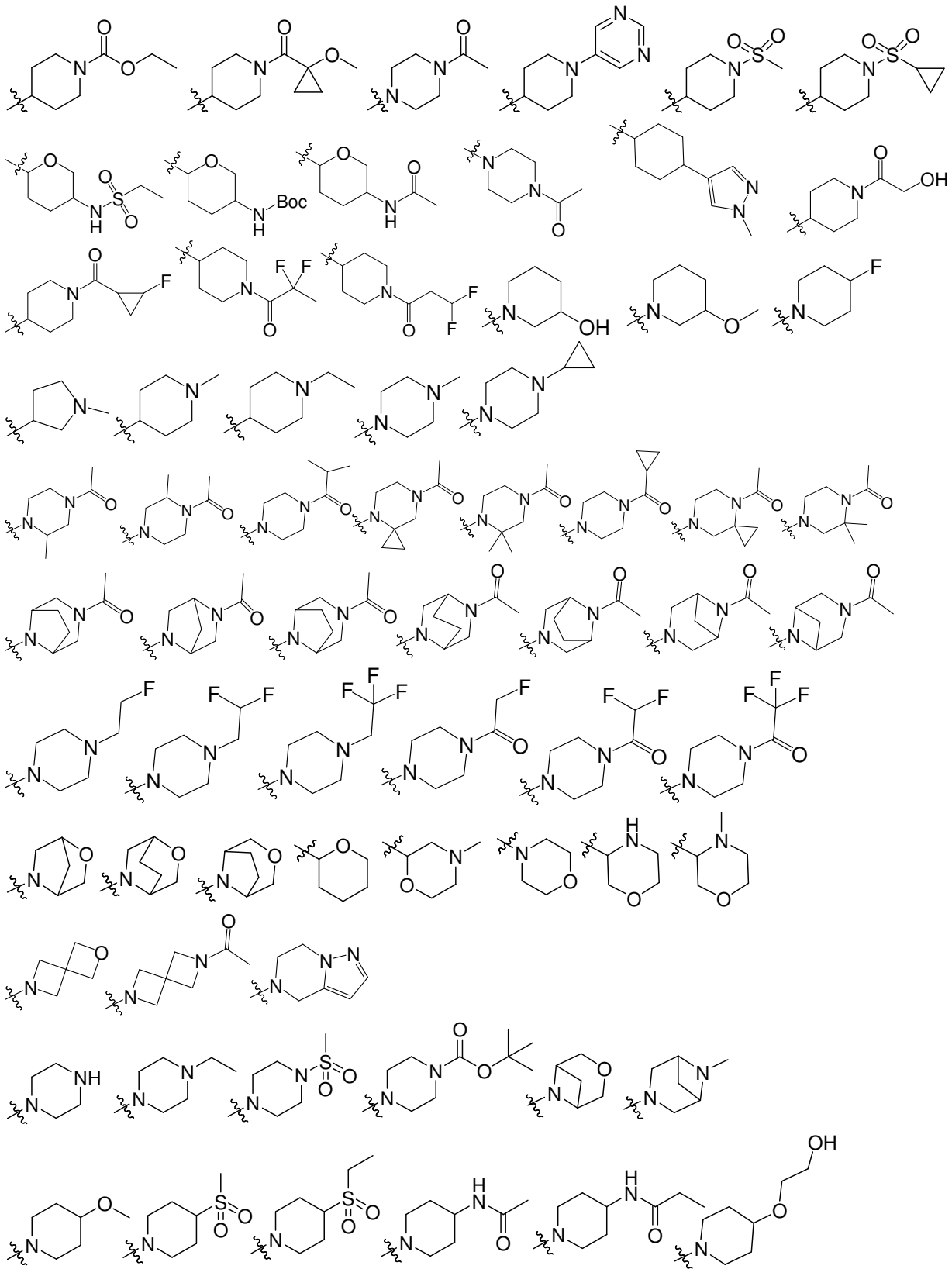








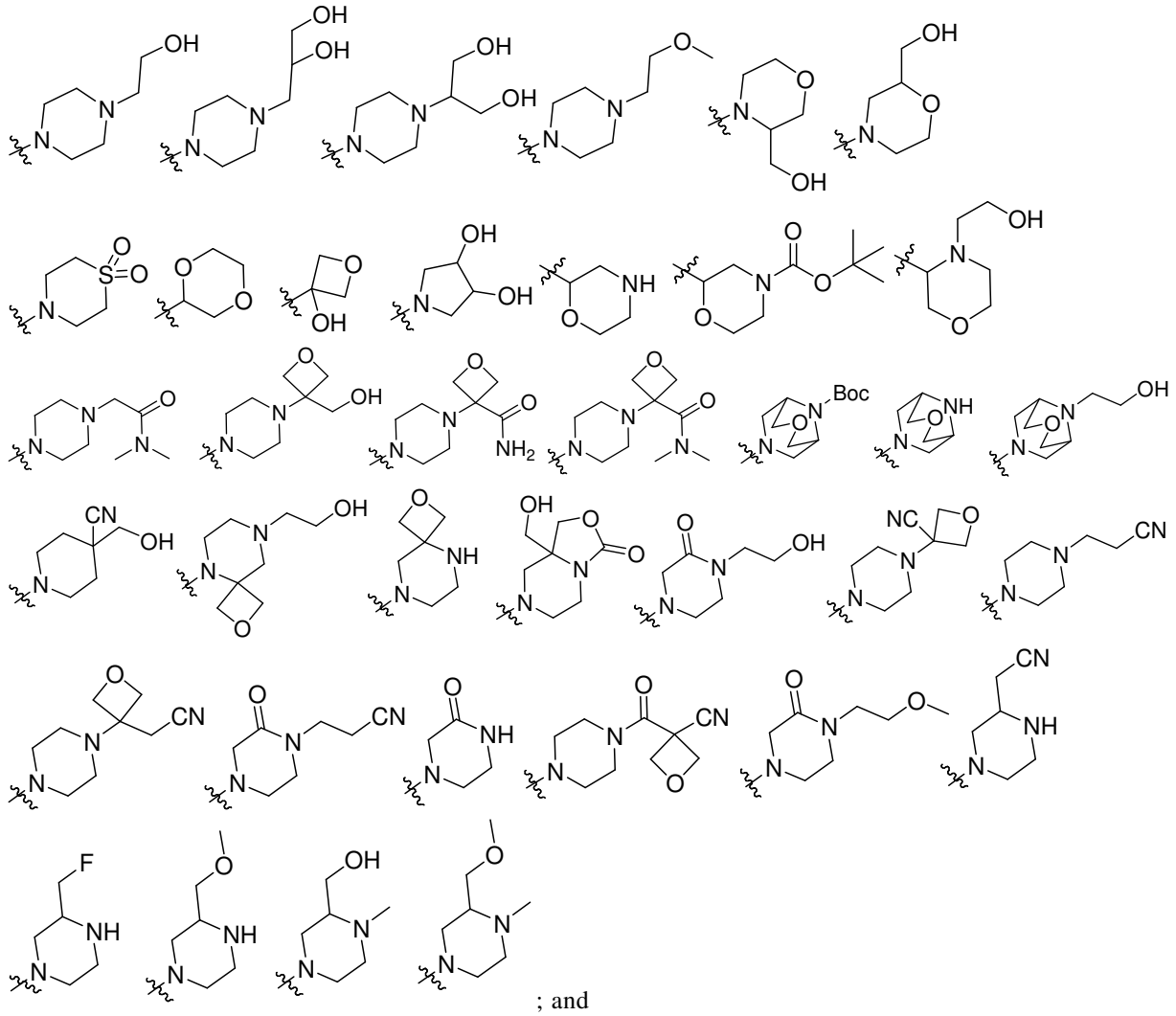
and ;

preferably, in Y1, R^{Y0} is selected from the group consisting of: H, halogen, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy;

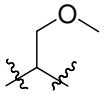
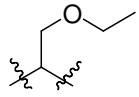
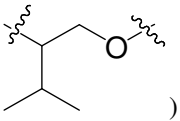
more preferably, Y1 is selected from the group consisting of:







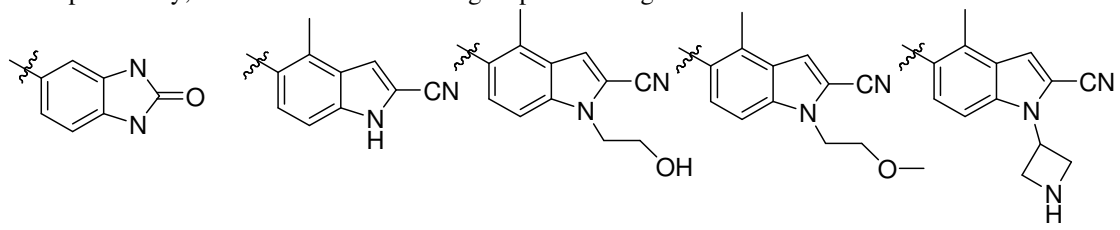
; and

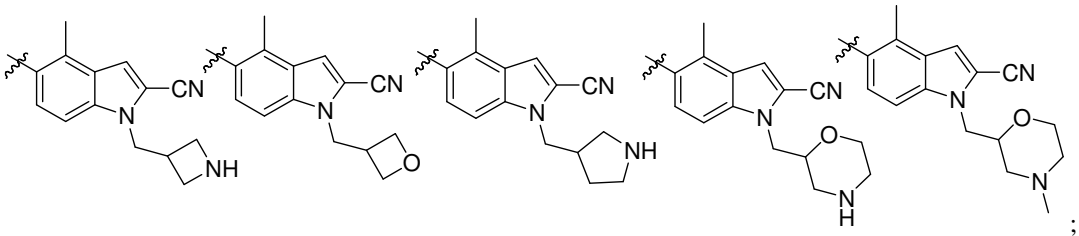
preferably, L_2 is C_1-C_6 alkylene, alkoxy-substituted C_1-C_6 alkylene (for example,  and ), -N(C_0-C_3 alkyl)-(C_0-C_6 alkylene)-, or -(C_0-C_6 alkylene)-O- (for example, ).

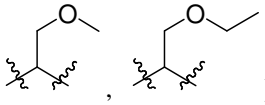
14.The compound according to claim 12, wherein R^{Y2} is selected from the group consisting of: H, -(C_1-C_4 alkylene)-OH, -(C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -(C_0-C_4 alkylene)-(C_3-C_6 cycloalkyl), and -(C_0-C_4 alkylene)-(optionally substituted 4-10-membered heterocyclyl);

preferably, in Y2, R^{Y0} is selected from the group consisting of: H, halogen, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy;

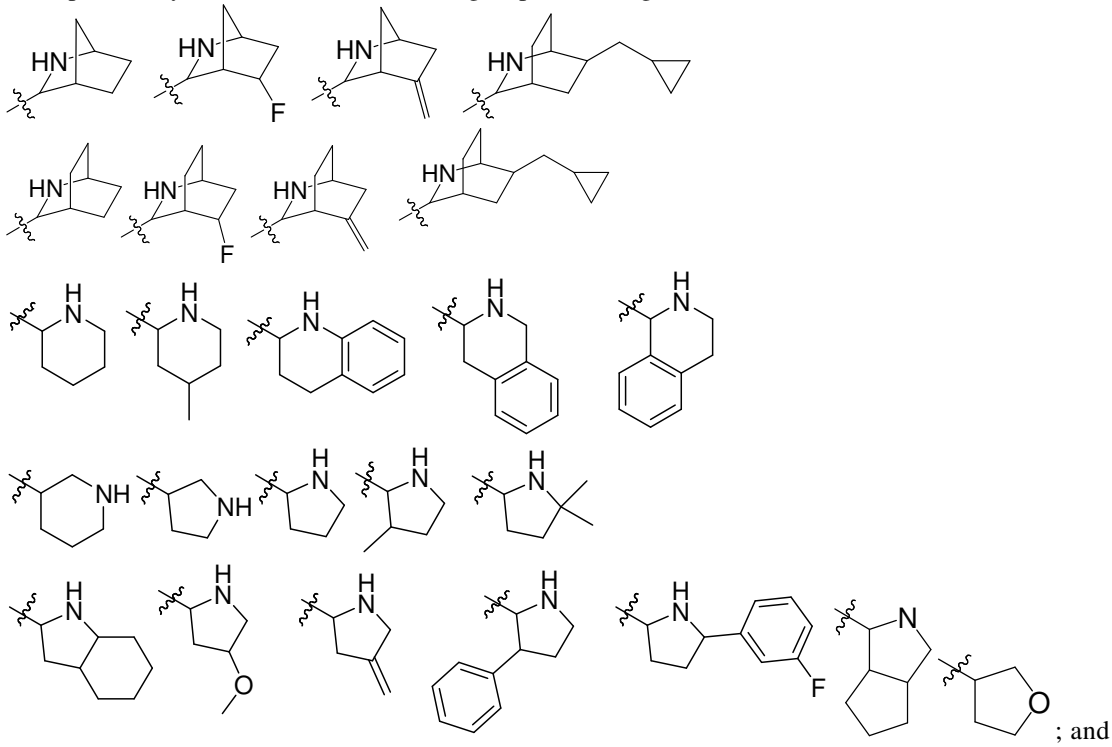
more preferably, Y2 is selected from the group consisting of:



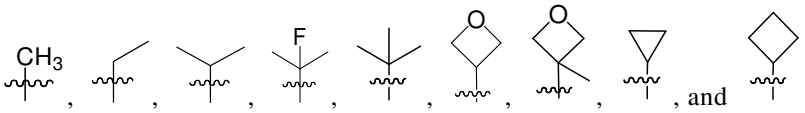

; and

preferably, L_2 is C_1-C_6 alkylene, alkoxy-substituted C_1-C_6 alkylene (for example, ) or -N(C_0-C_3 alkyl)-(C_0-C_6 alkylene)-.

15.The compound according to claim 12, wherein R^{Y3} is selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, and halogenated phenyl;
preferably, in Y3, R^{Y0} is selected from the group consisting of: H, halogen, C_1-C_3 alkyl, halogenated C_1-C_3 alkyl, hydroxyl, and C_1-C_3 alkoxy;
more preferably, Y3 is selected from the group consisting of:

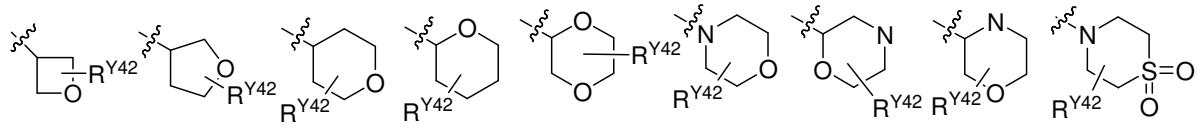
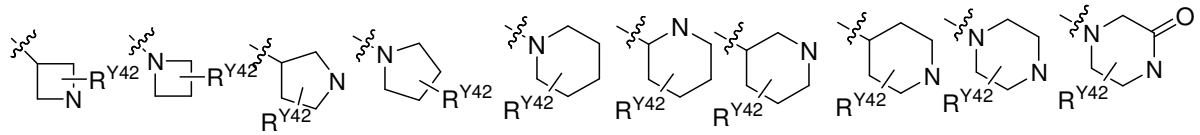

; and

preferably, L_2 is C(O).

16.The compound according to claim 12, wherein R^{Y40} is C_1-C_4 alkyl, halogenated C_1-C_4 alkyl or 3-6-membered heterocyclyl optionally substituted with C_1-C_3 alkyl, preferably selected from the group consisting of:  ;
preferably, Z' is a single bond, C_1-C_6 alkylene or C_3-C_6 cycloalkylene, wherein H in said alkylene is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, and hydroxyl;
preferably, R^{Y41} is selected from the group consisting of: -N($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CO($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)CON($C_{0\text{-}10}$ alkyl), -N($C_{0\text{-}10}$ alkyl)SO_2($C_{0\text{-}10}$ alkyl), -O($C_{0\text{-}10}$ alkyl), -COO($C_{0\text{-}10}$ alkyl), -OCO($C_{0\text{-}10}$ alkyl), and -CON($C_{0\text{-}10}$ alkyl)($C_{0\text{-}10}$ alkyl); wherein H in said alkyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, and C_1-C_6 alkoxy; or,

R^{Y41} is 4-12-membered heterocyclyl, H in said heterocyclyl is optionally substituted with one or more R^{Y42}, each R^{Y42} is independently selected from the group consisting of: H, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_3-C_6 cycloalkyl, 4-6-membered saturated heterocyclyl, -N(C_{0-6} alkyl)(C_{0-6} alkyl), -N(C_{0-6} alkyl)CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)CON(C_{0-6} alkyl), -N(C_{0-6} alkyl)SO_2(C_{0-6} alkyl), -O(C_{0-6} alkyl), -S(C_{0-6} alkyl), -SO(C_{0-6} alkyl), -SO_2(C_{0-6} alkyl), -SO_2N(C_{0-6} alkyl)(C_{0-6} alkyl), -COO(C_{0-6} alkyl), -OCO(C_{0-6} alkyl), -CON(C_{0-6} alkyl)(C_{0-6} alkyl), -CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)(4-6-membered heterocyclyl), -SO_2(4-6-membered heterocyclyl), -COO(4-6-membered heterocyclyl), -OCO(4-6-membered heterocyclyl), -CON(C_{0-6} alkyl)(4-6-membered heterocyclyl), and -CO(4-6-membered heterocyclyl); wherein H in said alkyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, C_1-C_6 alkyl, halogenated C_1-C_6 alkyl, C_1-C_6 hydroxylalkyl, C_1-C_6 alkoxyalkyl, C_1-C_6 cyanoalkyl, -N(C_{0-6} alkyl)(C_{0-6} alkyl), -N(C_{0-6} alkyl)CO(C_{0-6} alkyl), -N(C_{0-6} alkyl)CON(C_{0-6} alkyl), -N(C_{0-6} alkyl)SO_2(C_{0-6} alkyl), -O(C_{0-6} alkyl), -S(C_{0-6} alkyl), -SO(C_{0-6} alkyl), -SO_2(C_{0-6} alkyl), -SO_2N(C_{0-6} alkyl)(C_{0-6} alkyl), -COO(C_{0-6} alkyl), -OCO(C_{0-6} alkyl), -CON(C_{0-6} alkyl)(C_{0-6} alkyl), and -CO(C_{0-6} alkyl);

more preferably, R^{Y41} is selected from the group consisting of: -N(C_{0-10} alkyl)(C_{0-10} alkyl), -O(C_{0-10} alkyl), and -COO(C_{0-10} alkyl); wherein H in said alkyl is optionally substituted with one or more groups selected from the group consisting of: hydroxyl and C_1-C_3 alkoxy; or, R^{Y41} is selected from the group consisting of:


,

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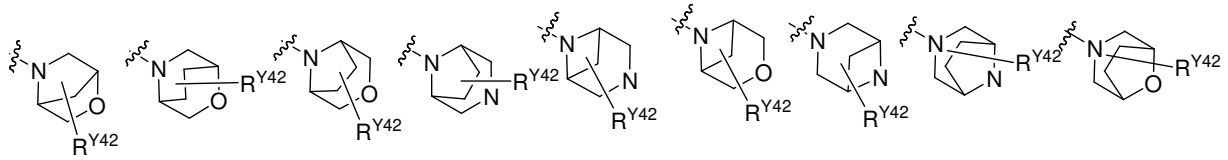
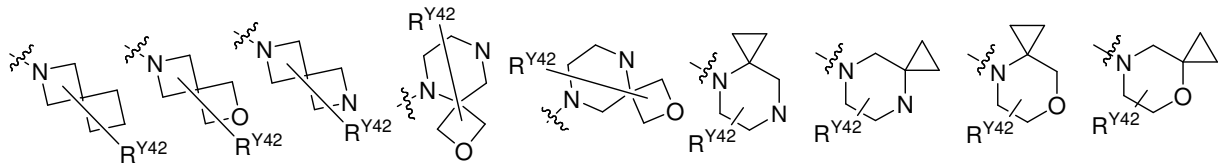
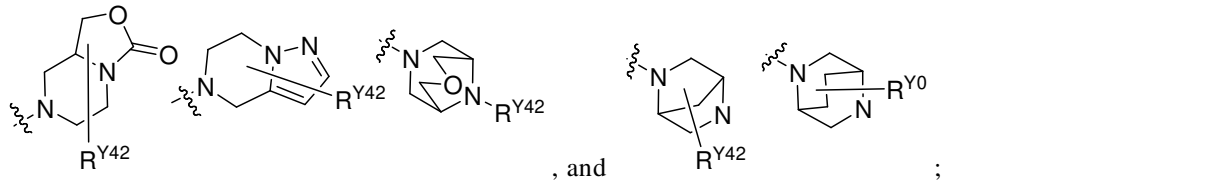
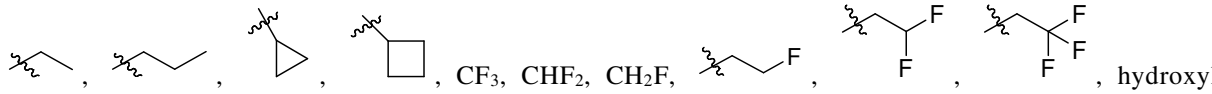
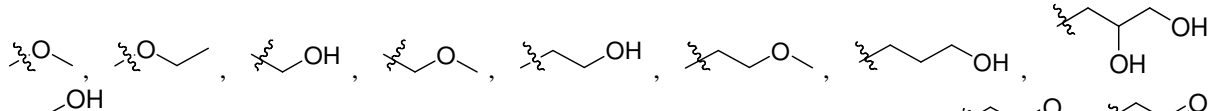
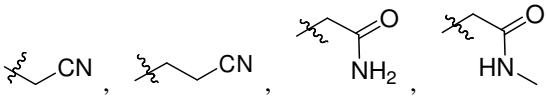
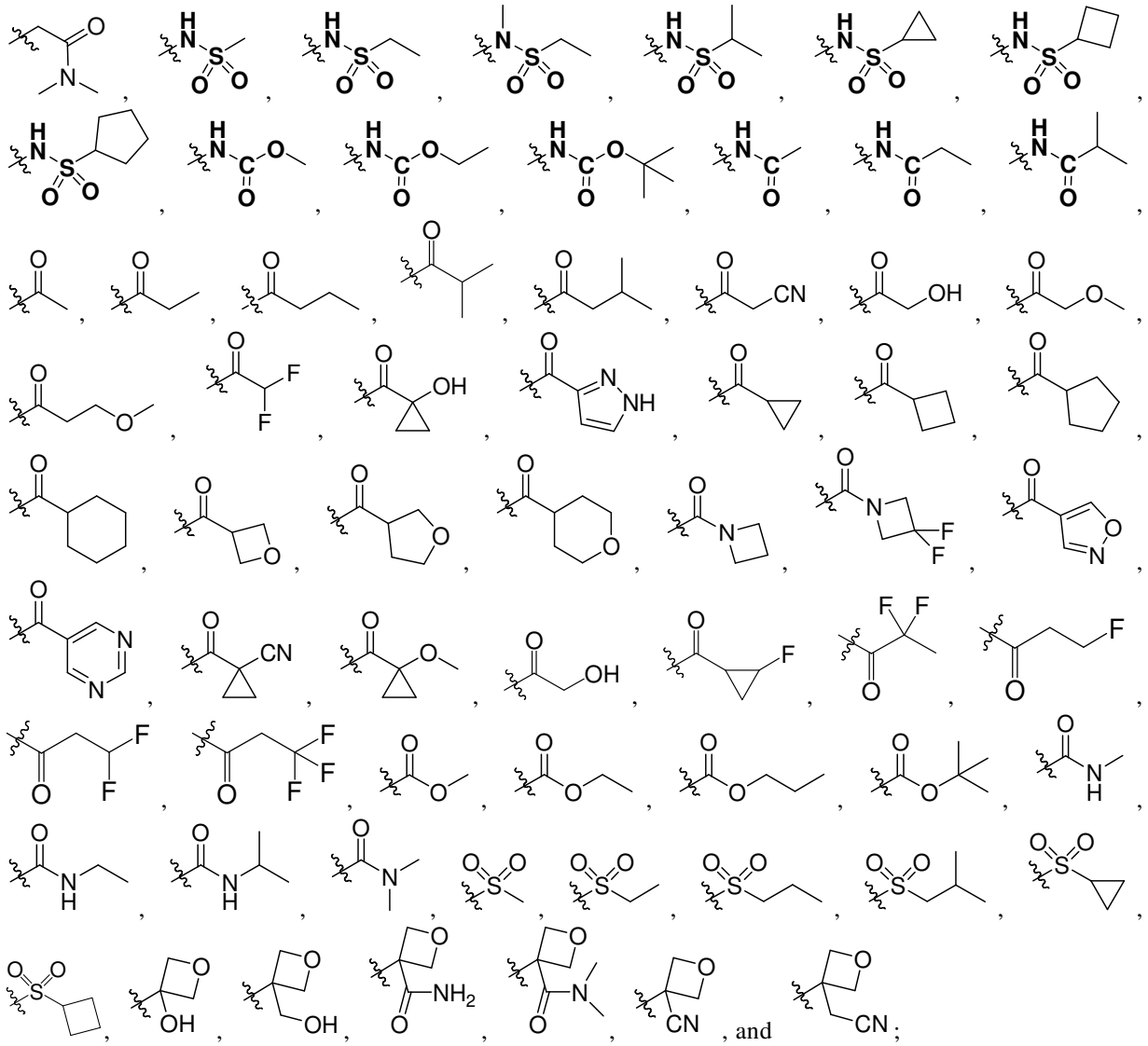
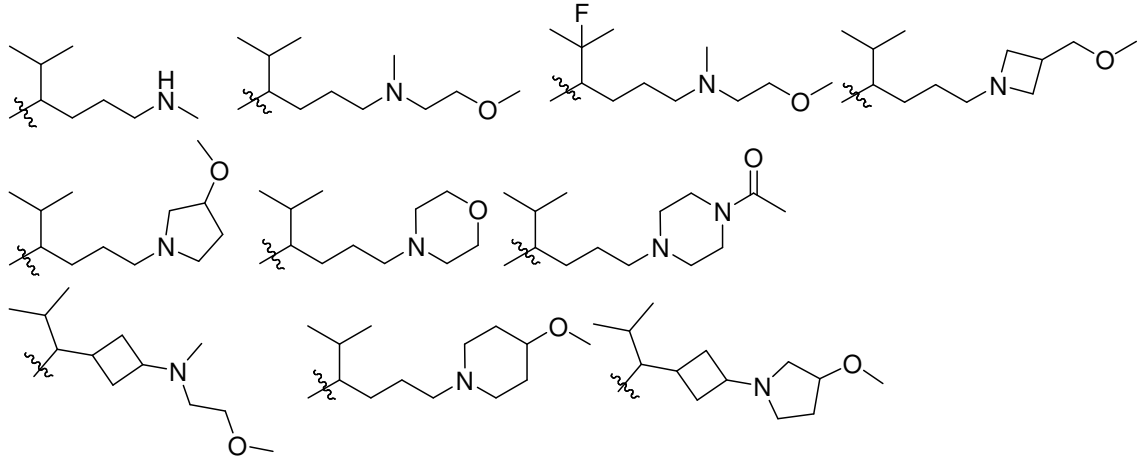
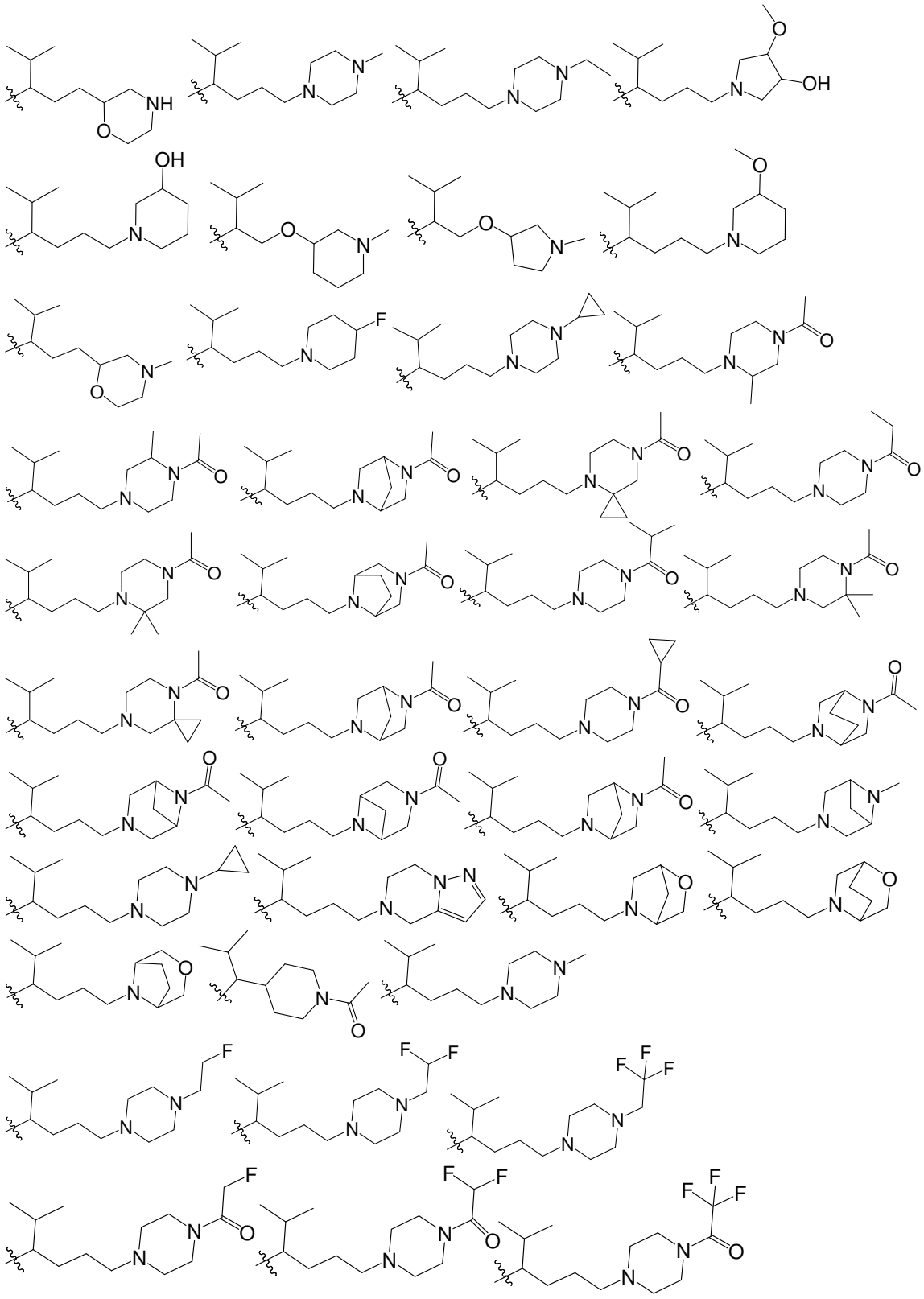

,

,

, and ;

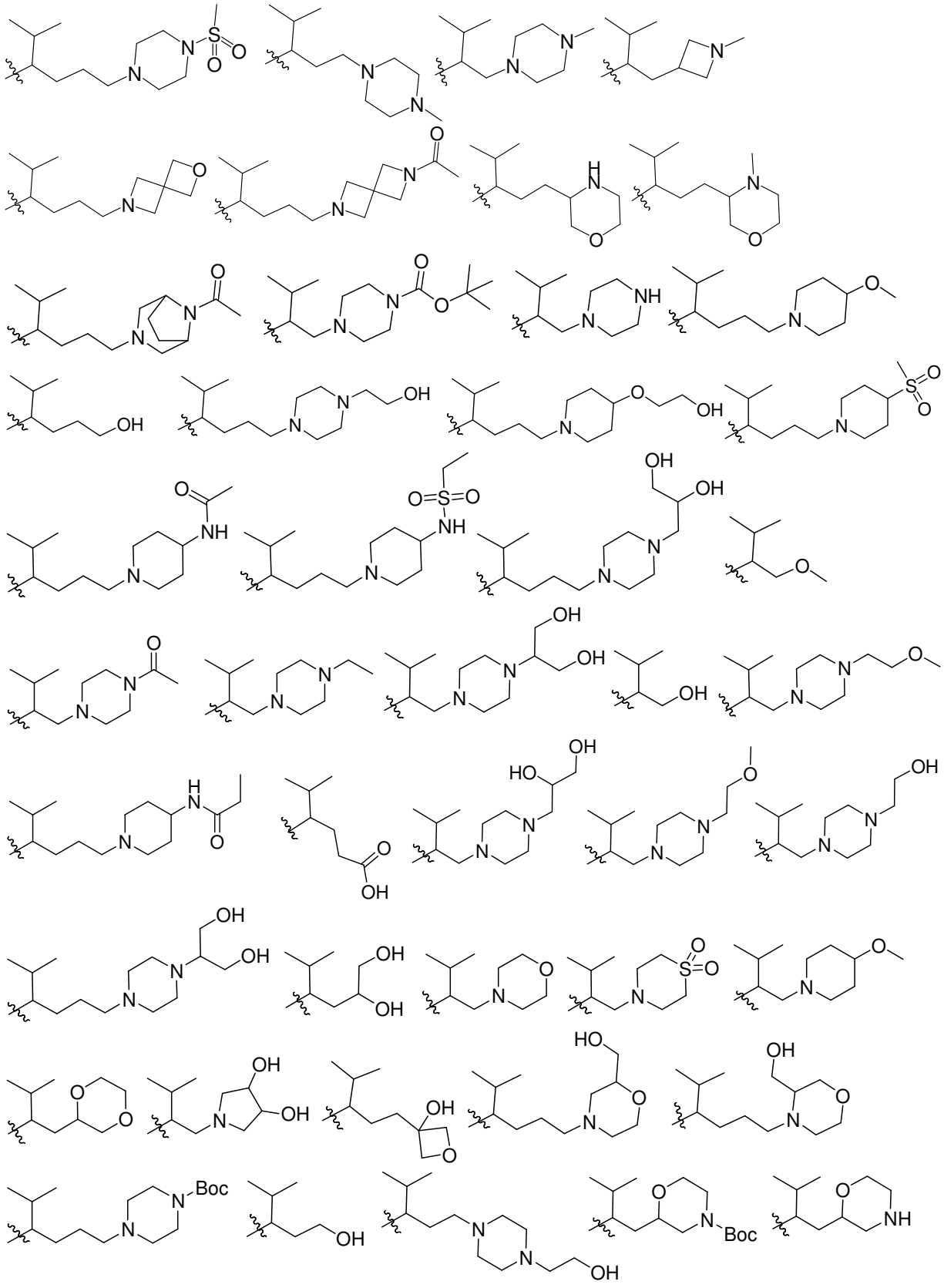
more preferably, each R^{Y42} is independently selected from the group consisting of: H, halogen, ,  , CF_3, CHF_2, CH_2F, , hydroxyl,  , cyano,  ,

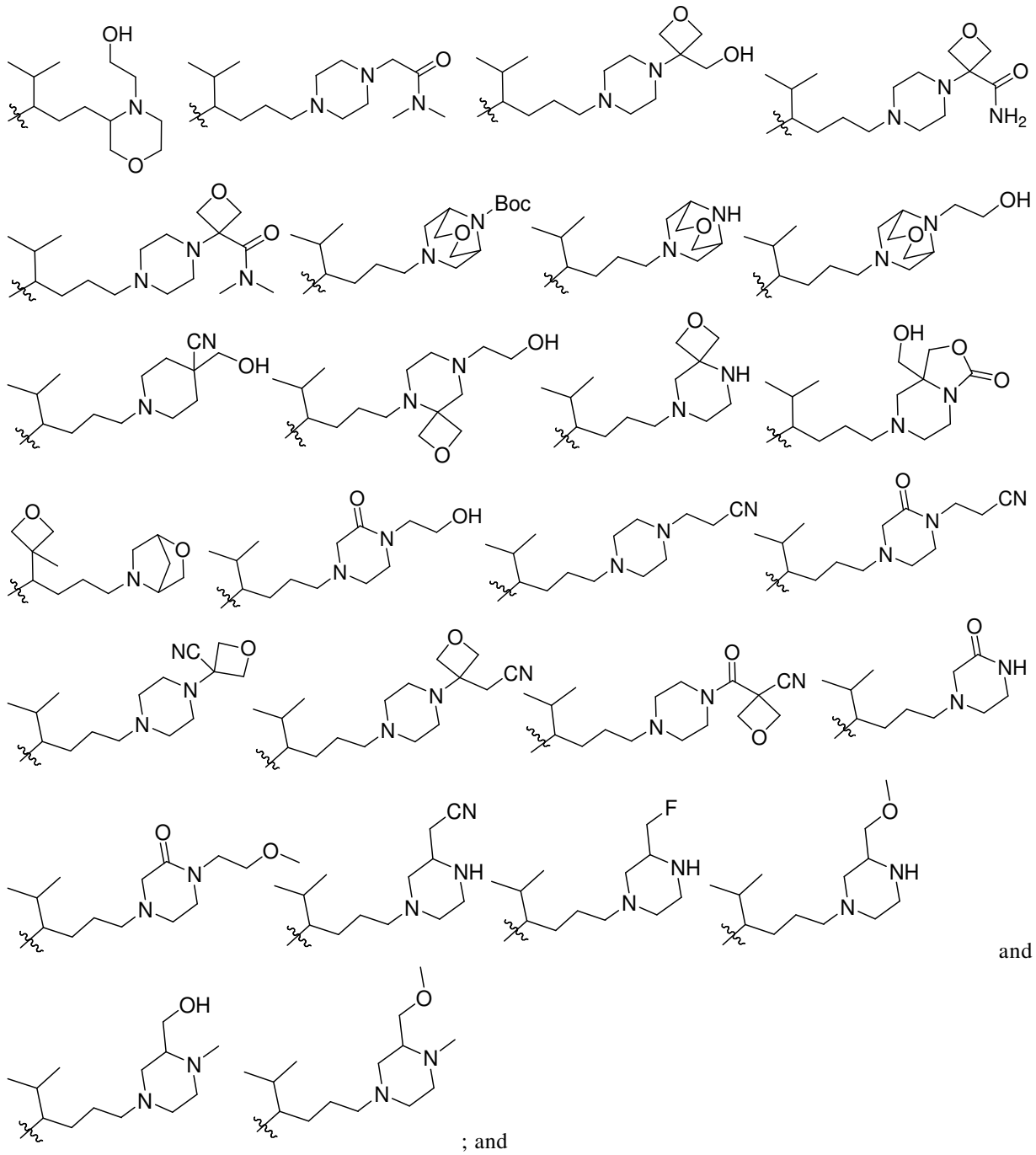


preferably, Y4 is selected from the group consisting of:









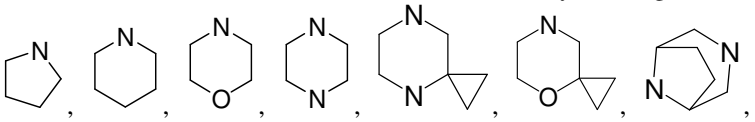
and

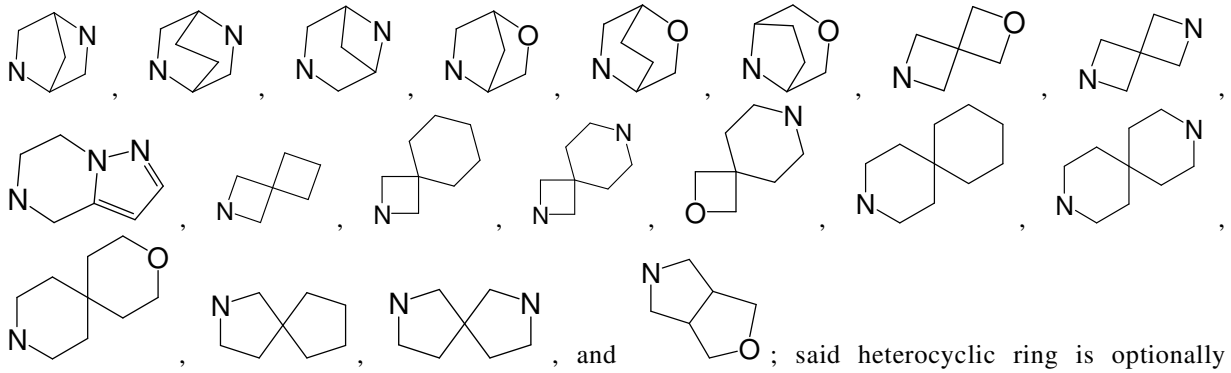
; and

preferably, L_2 is a single bond.

17.The compound according to claim 12, wherein R^{Y501} and R^{Y502} are independently selected from the group consisting of: C_1-C_3 alkyl, and halogenated C_1-C_3 alkyl; or, R^{Y501} and R^{Y502}, together with the carbon atom attached thereto, form C_3-C_6 cycloalkyl, and said C_3-C_6 cycloalkyl may be optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, hydroxyl, amino, C_1-C_3 alkoxy, and C_1-C_3 alkylamino;

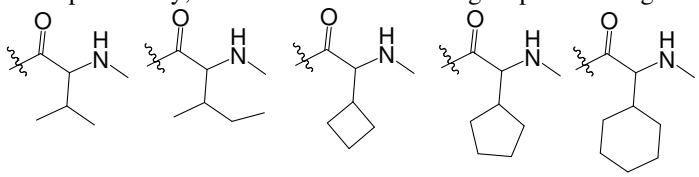
preferably, R^{Y503} is H, and R^{Y503} is C_1-C_3 alkyl; or,

R^{Y503} and R^{Y504}, together with the nitrogen atom attached thereto, form a saturated heterocyclic ring, which is selected from the group consisting of:  ,


; said heterocyclic ring is optionally substituted with one or more R^{Y505} groups;

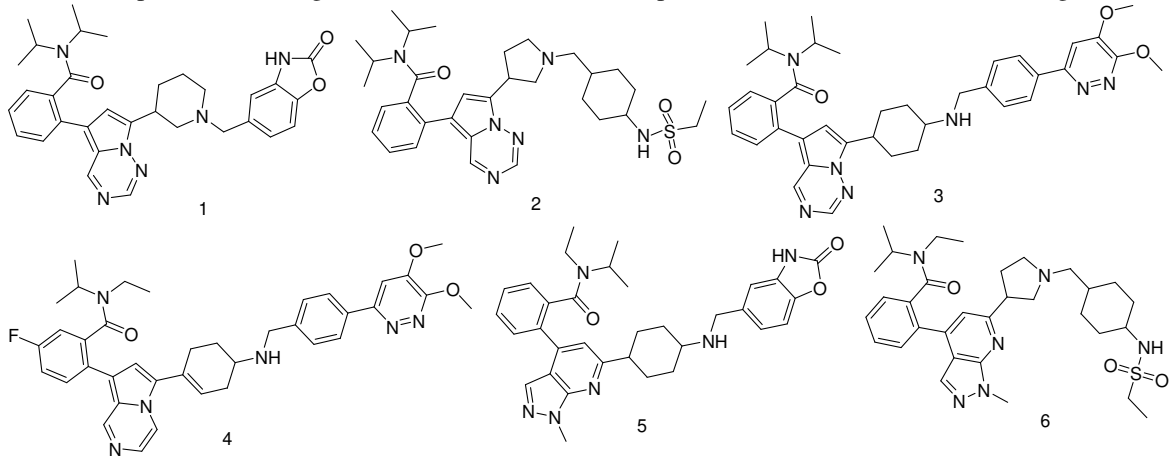
R^{Y505} is selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(C_0-C_6 alkylene)-(C_3-C_{10} cycloalkyl), -(C_0-C_6 alkylene)-(phenyl), -(C_0-C_6 alkylene)-(4-10-membered heterocyclyl), halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N(C_{0-10} alkyl)(C_{0-10} alkyl), -N(C_{0-10} alkyl)CO(C_{0-10} alkyl), -N(C_{0-10} alkyl)CON(C_{0-10} alkyl), -N(C_{0-10} alkyl)SO_2(C_{0-10} alkyl), -O(C_{0-10} alkyl), -S(C_{0-10} alkyl), -SO(C_{0-10} alkyl), -SO_2(C_{0-10} alkyl), -SO_2N(C_{0-10} alkyl)(C_{0-10} alkyl), -COO(C_{0-10} alkyl), -OCO(C_{0-10} alkyl), -CON(C_{0-10} alkyl)(C_{0-10} alkyl), -CO(C_{0-10} alkyl), and -CO(C_3-C_{10} cycloalkyl); wherein H in said C_{0-10} alkyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_0-C_6 alkylene, C_3-C_{10} cycloalkyl, phenyl, or 4-10-membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of: halogen, cyano, nitro, azido, C_1-C_{10} alkyl, halogenated C_1-C_{10} alkyl, halogenated C_1-C_{10} alkoxy, -N(C_{0-10} alkyl)(C_{0-10} alkyl), -N(C_{0-10} alkyl)CO(C_{0-10} alkyl), -N(C_{0-10} alkyl)CON(C_{0-10} alkyl), -N(C_{0-10} alkyl)SO_2(C_{0-10} alkyl), -O(C_{0-10} alkyl), -S(C_{0-10} alkyl), -SO(C_{0-10} alkyl), -SO_2(C_{0-10} alkyl), -SO_2N(C_{0-10} alkyl)(C_{0-10} alkyl), -COO(C_{0-10} alkyl), -OCO(C_{0-10} alkyl), -CON(C_{0-10} alkyl)(C_{0-10} alkyl), and -CO(C_{0-10} alkyl); and

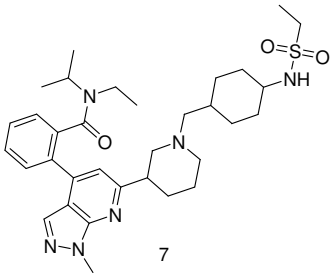
more preferably, Y5 is selected from the group consisting of:


;

preferably, said L_2 is C(O).

18.The compound according to claim 1, wherein said compound is selected from the following structures:





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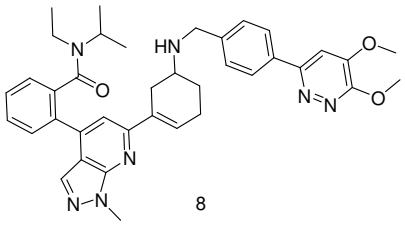

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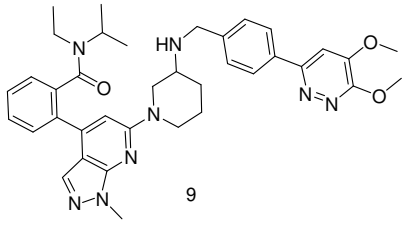

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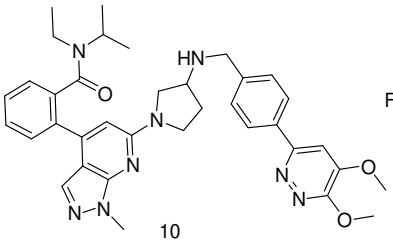

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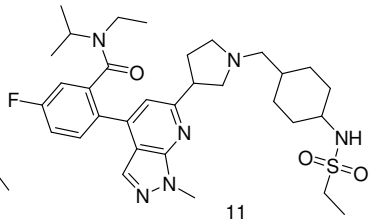

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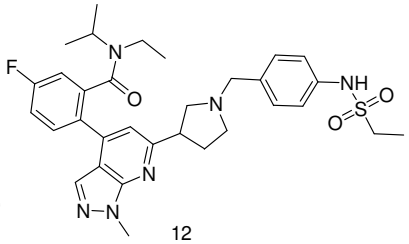

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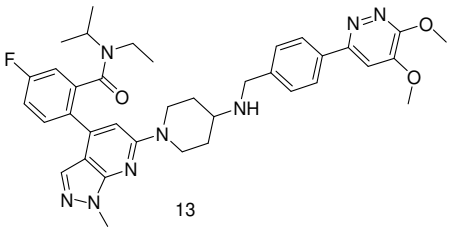

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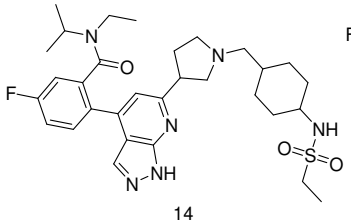

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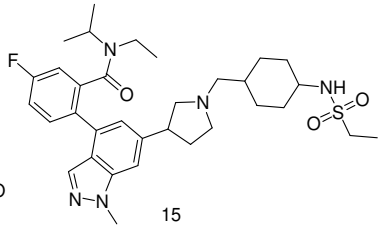

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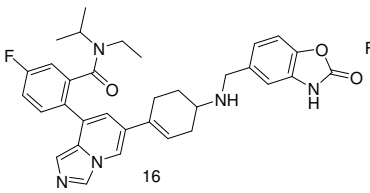

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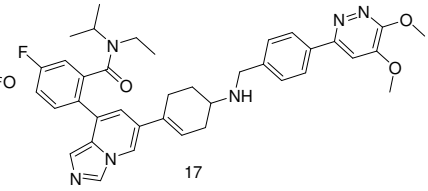

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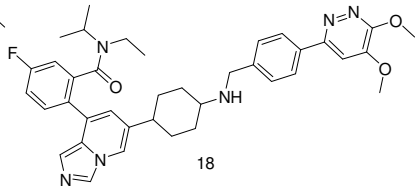

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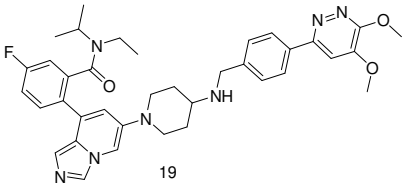

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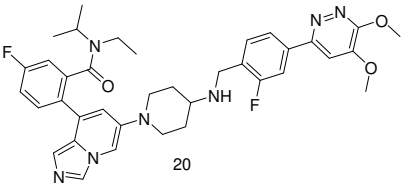

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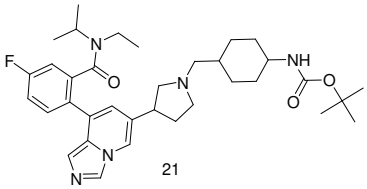

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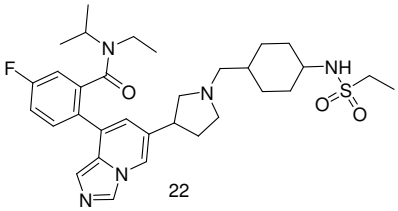

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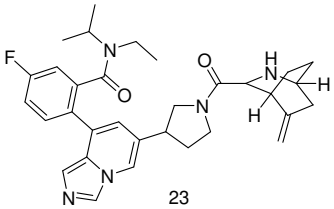

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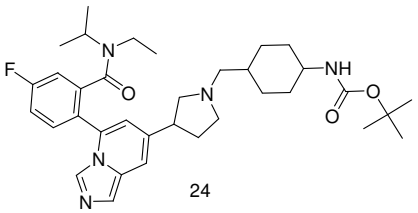

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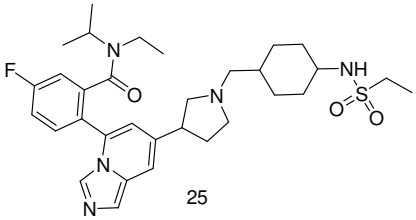

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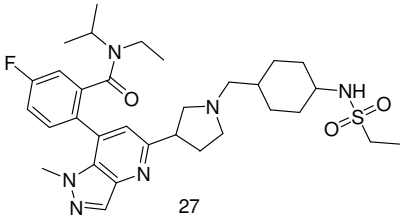

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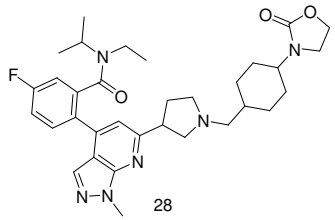

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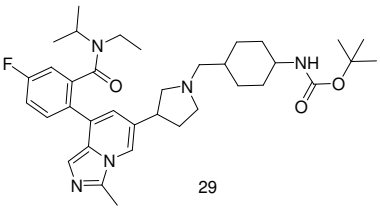

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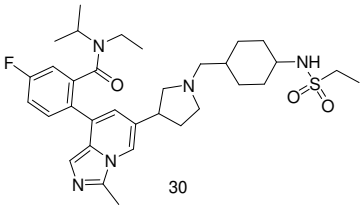

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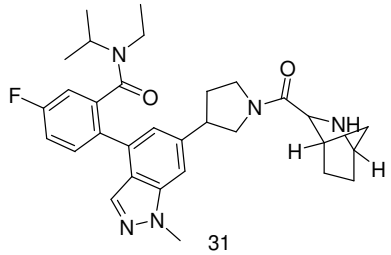

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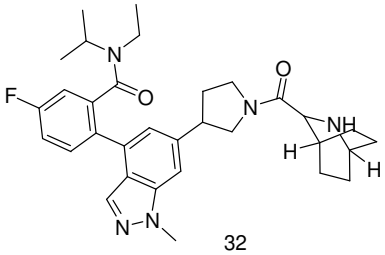

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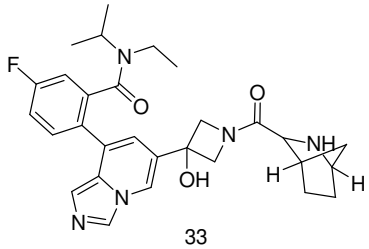

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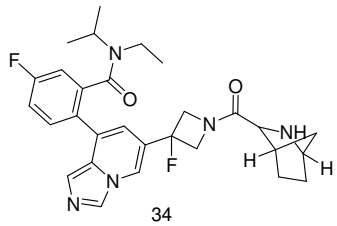

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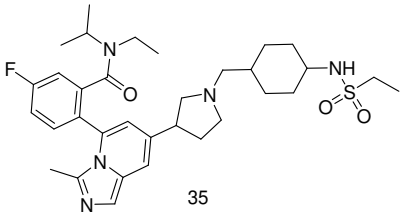

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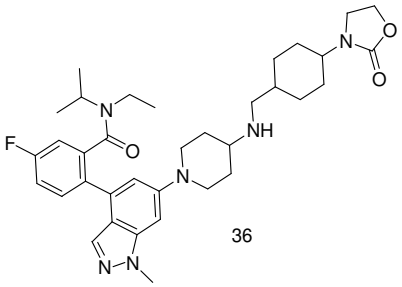

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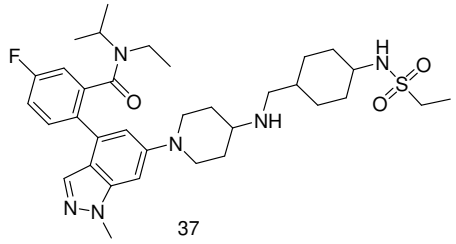

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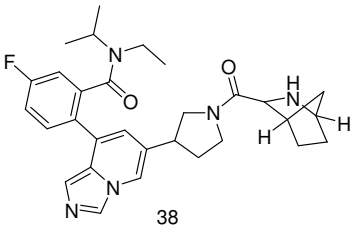

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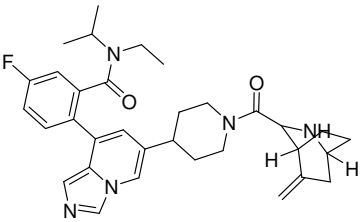

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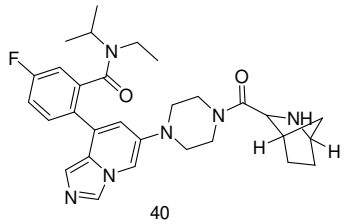

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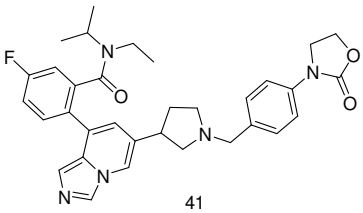

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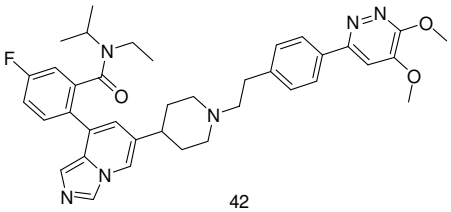

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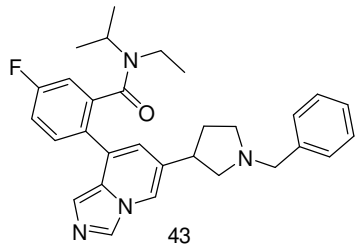

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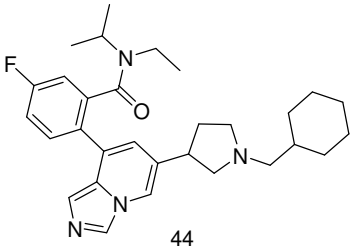

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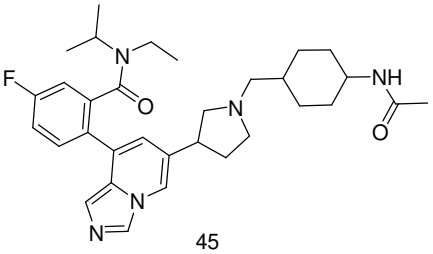

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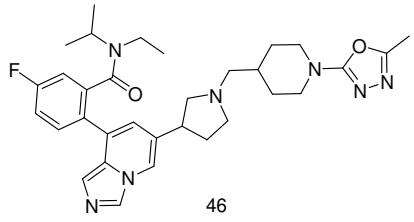

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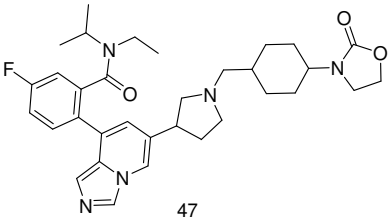

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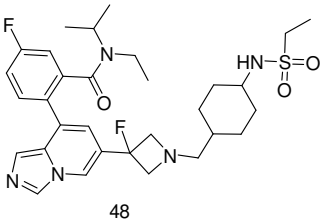

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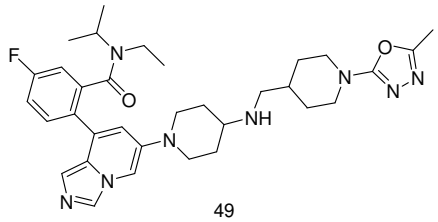

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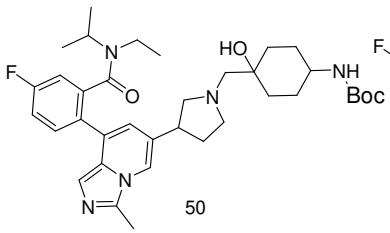

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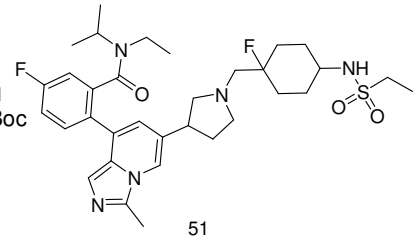

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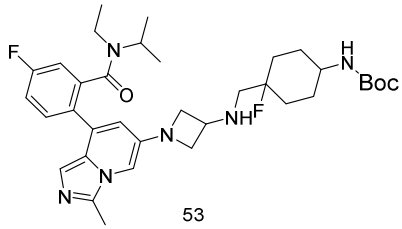

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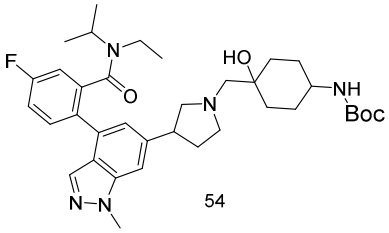

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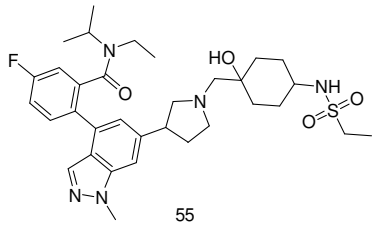

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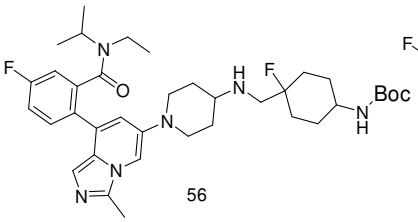

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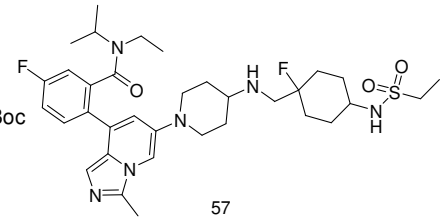

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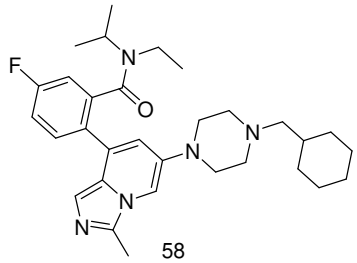

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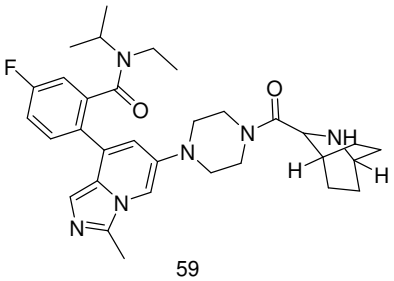

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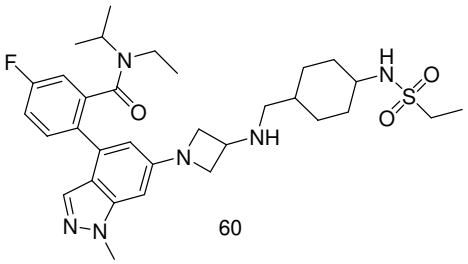

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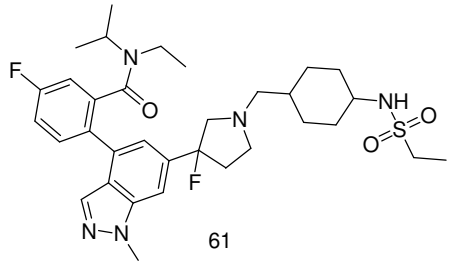

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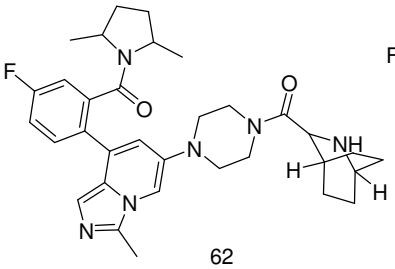

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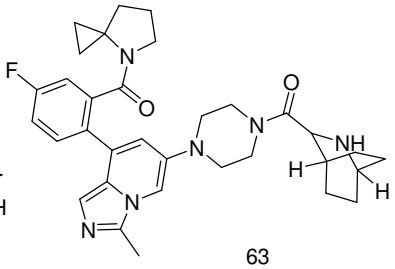

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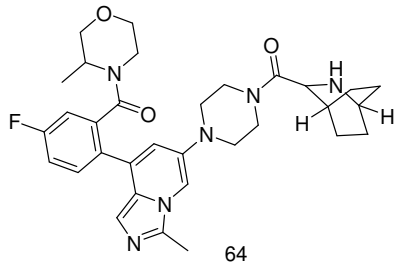

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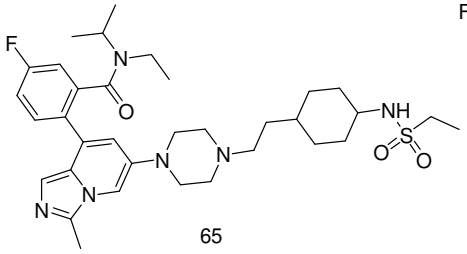

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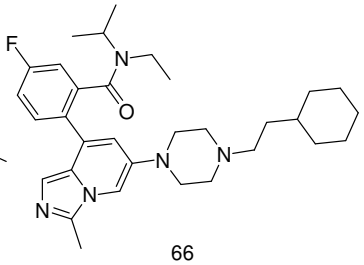

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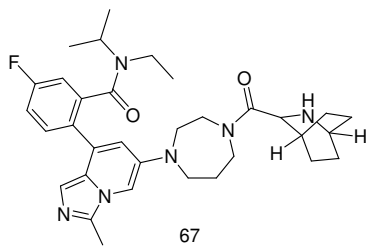

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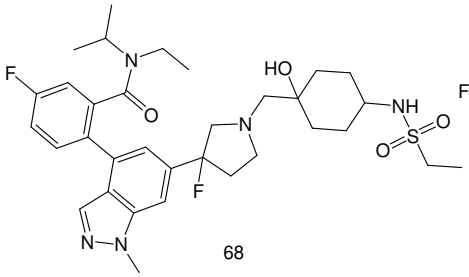

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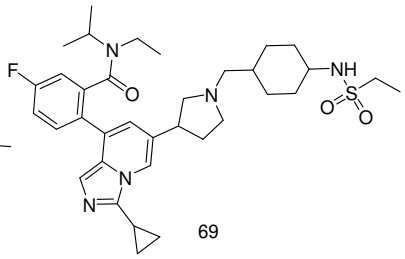

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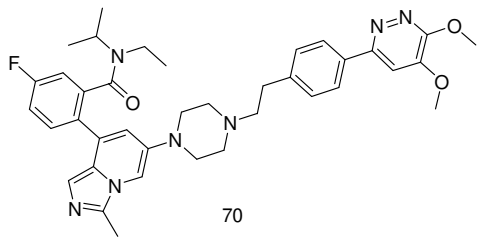

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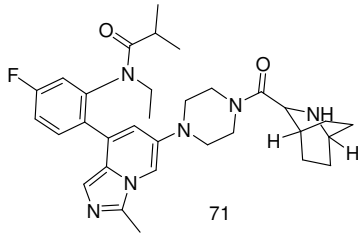

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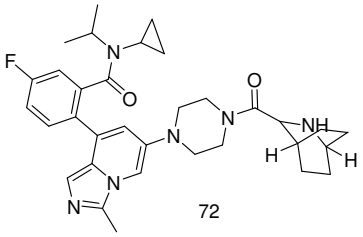

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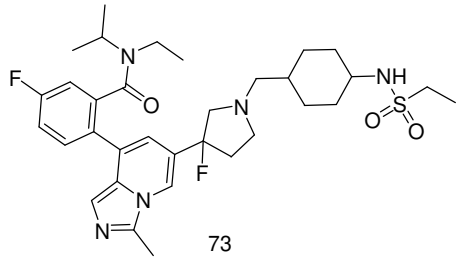

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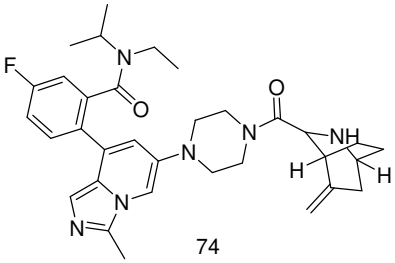

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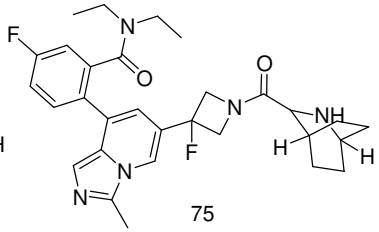

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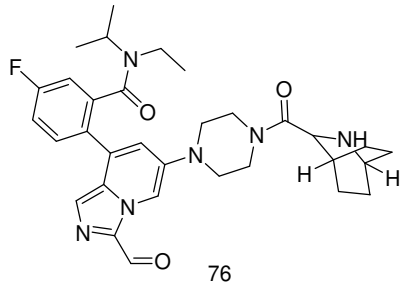

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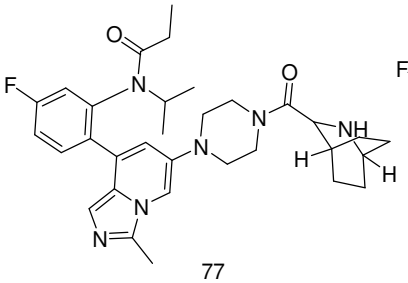

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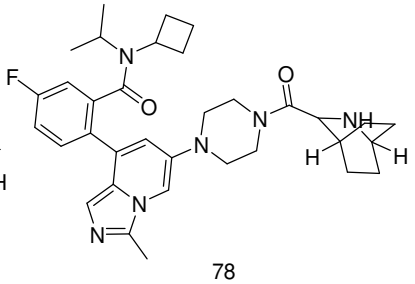

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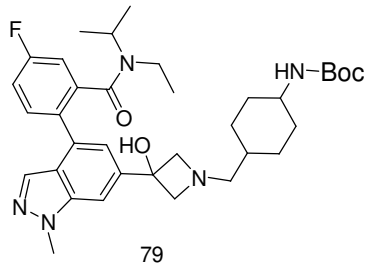

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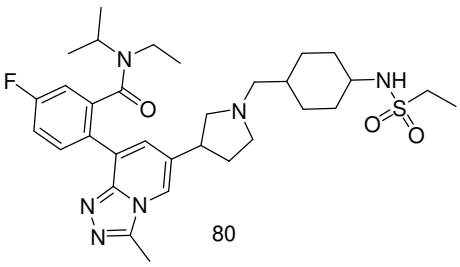

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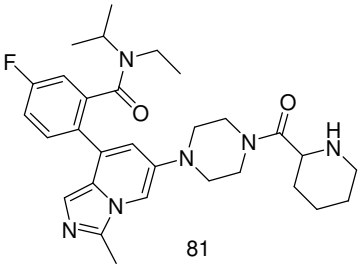

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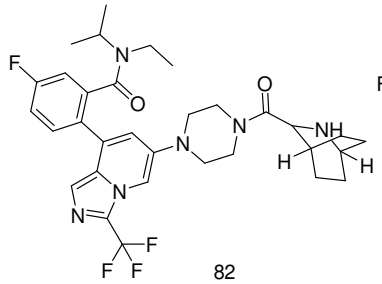

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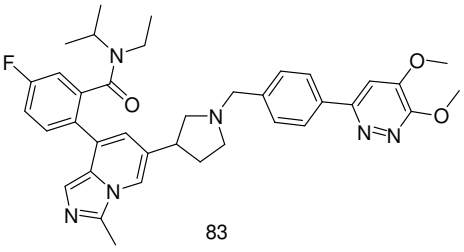

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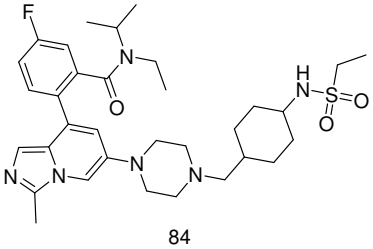

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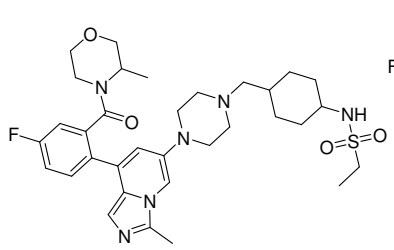

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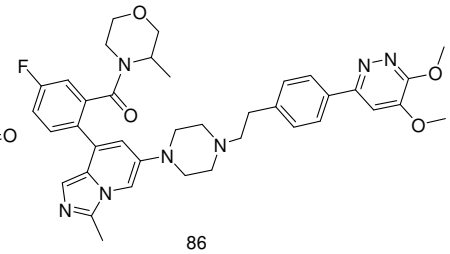

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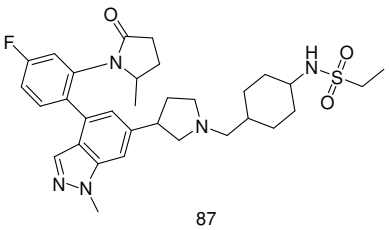

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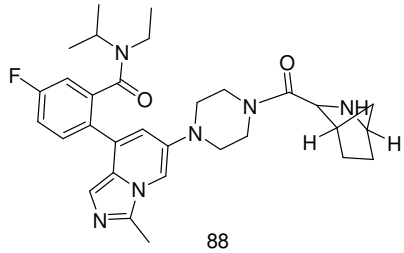

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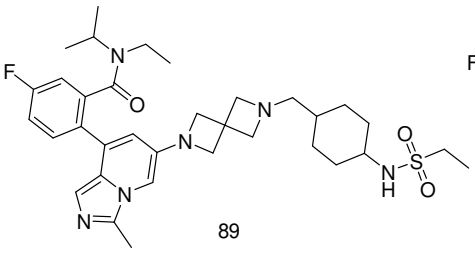

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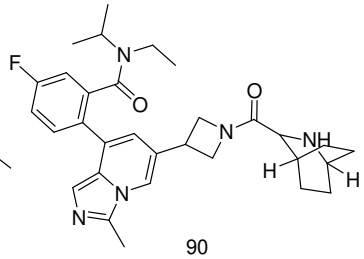

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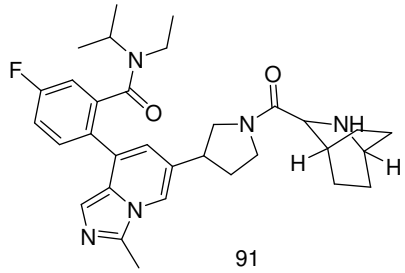

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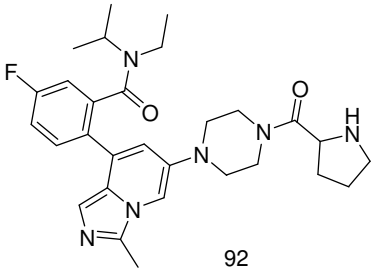

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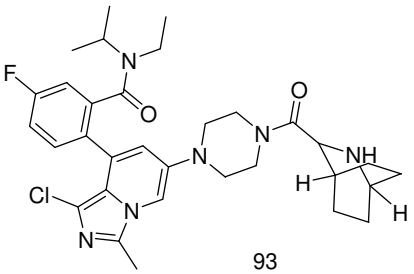

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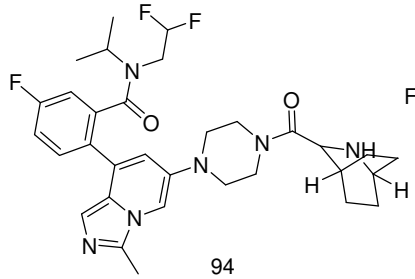

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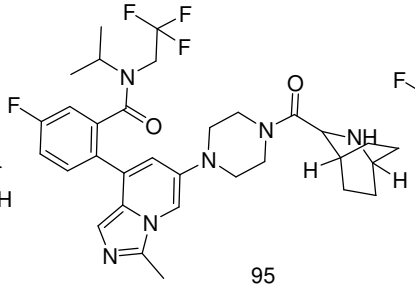

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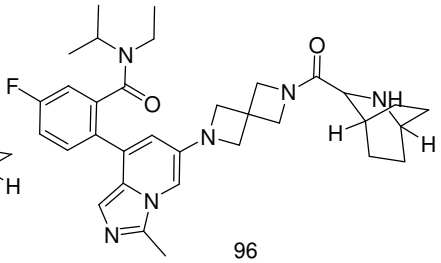

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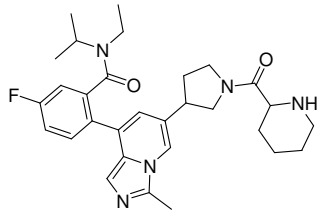

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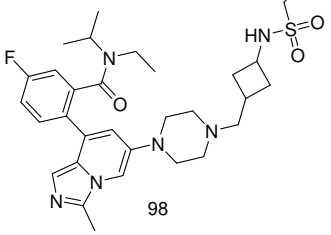

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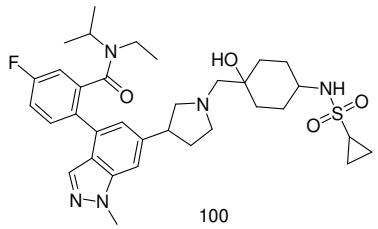

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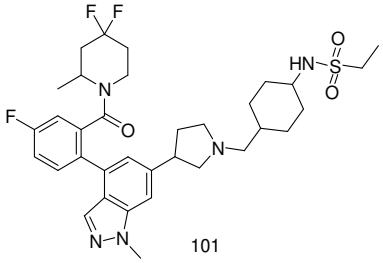

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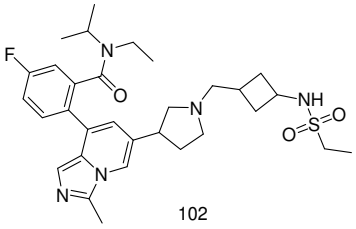

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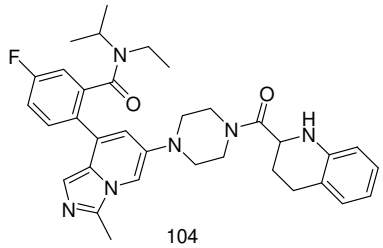

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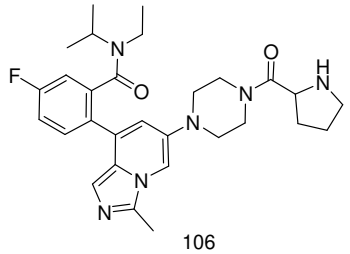

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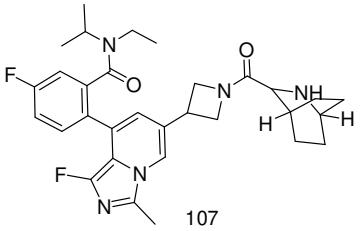

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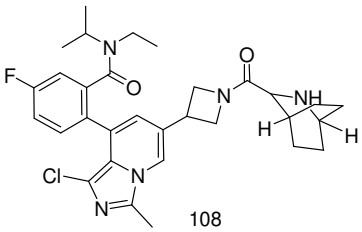

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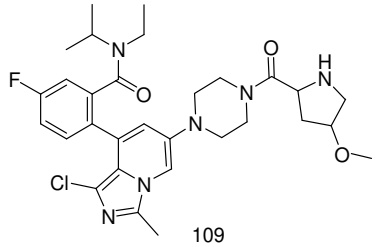

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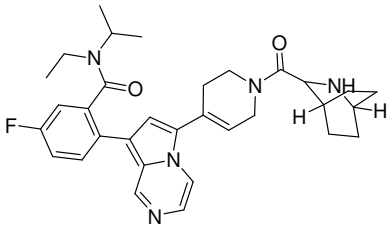

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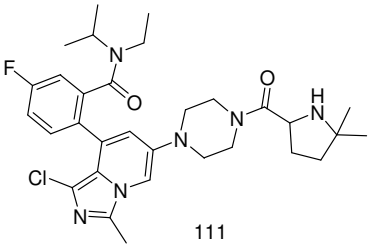

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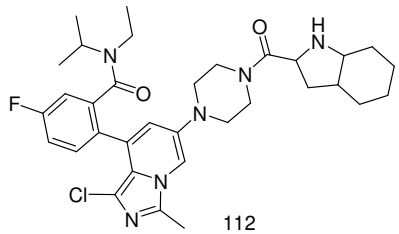

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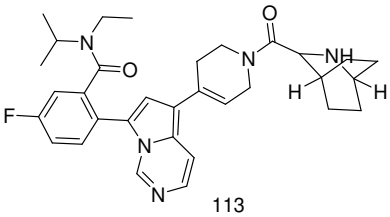

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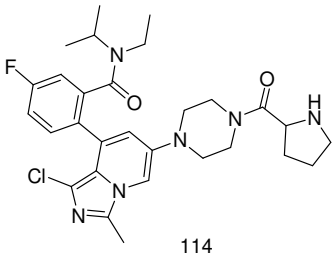

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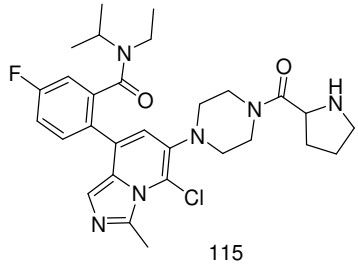

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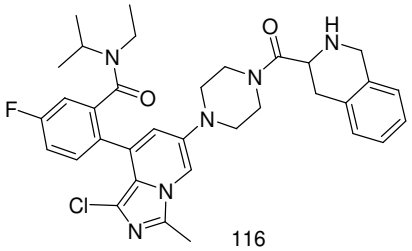

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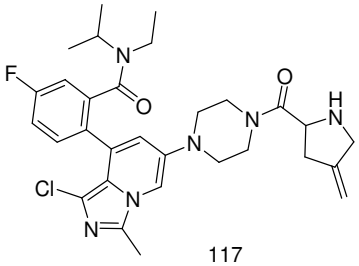

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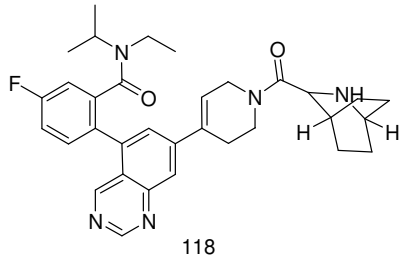

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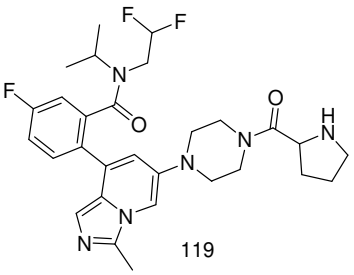

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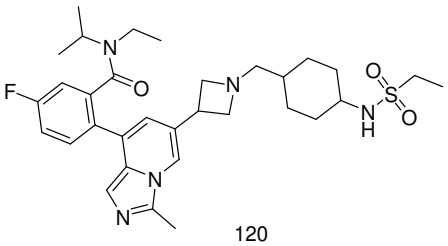

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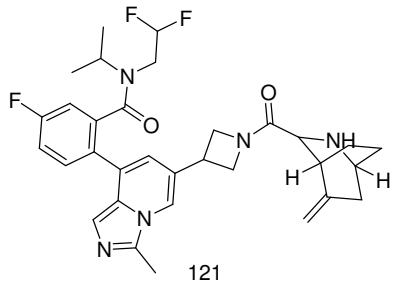

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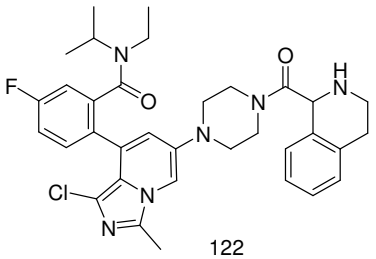

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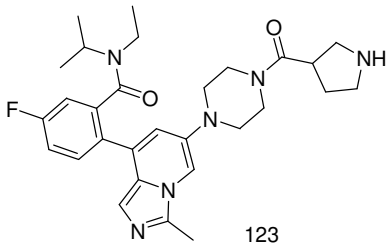

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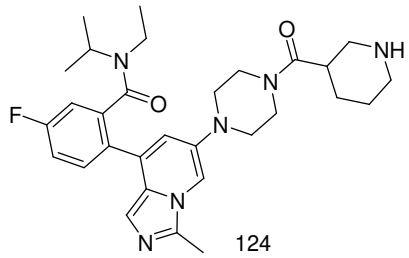

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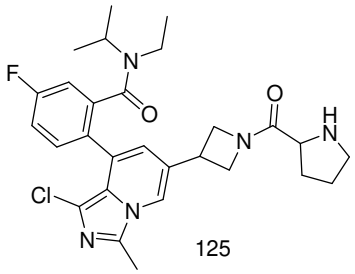

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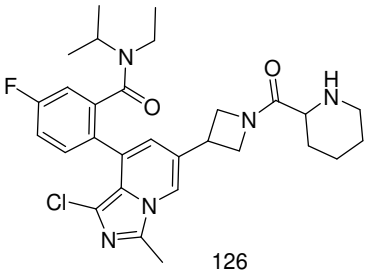

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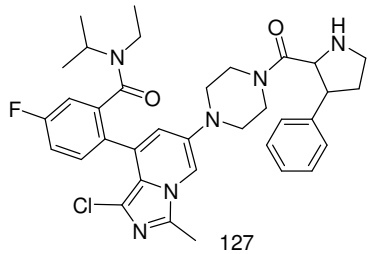

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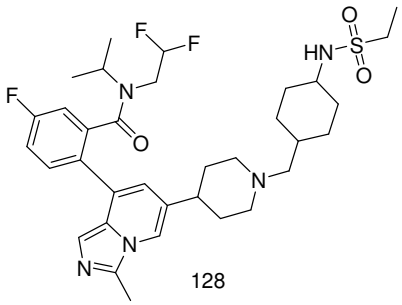

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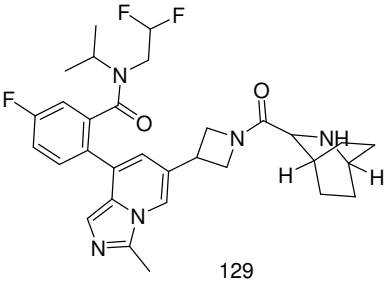

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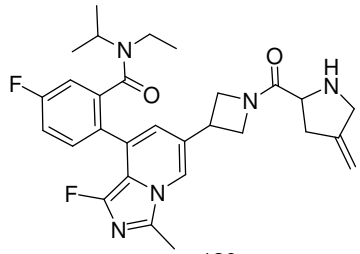

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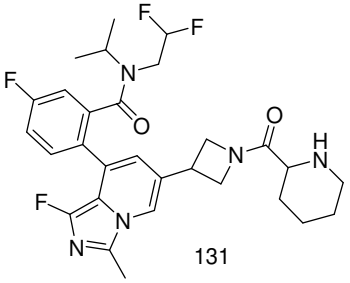

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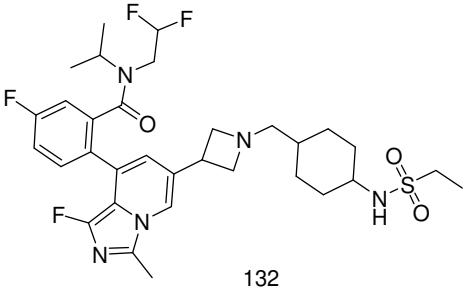

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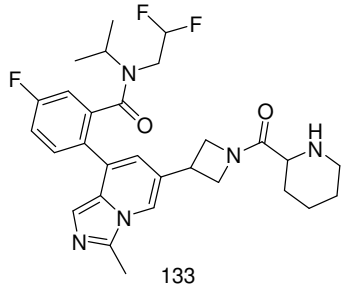

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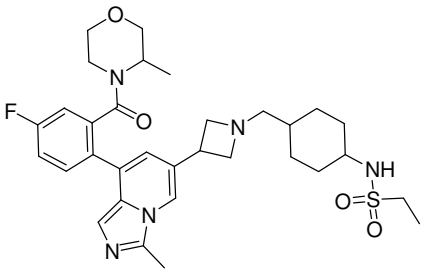

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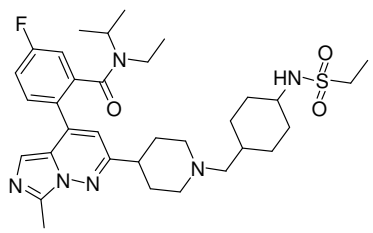

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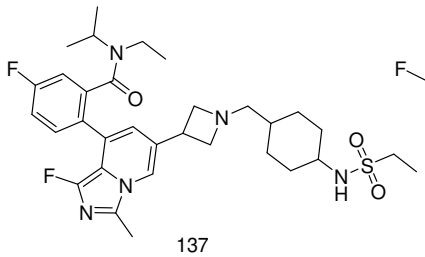

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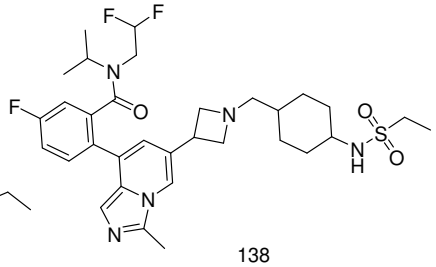

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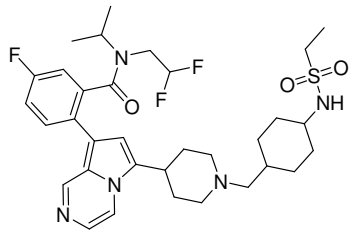

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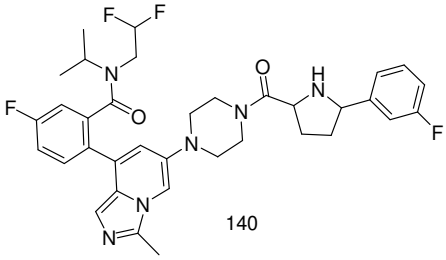

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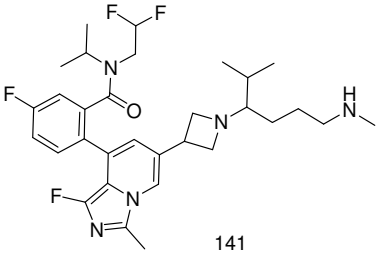

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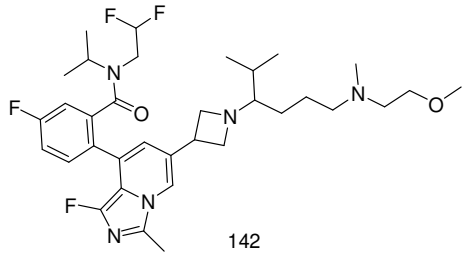

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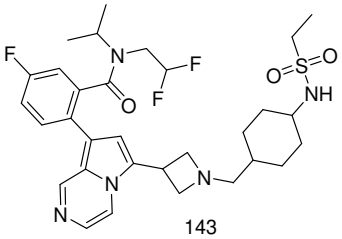

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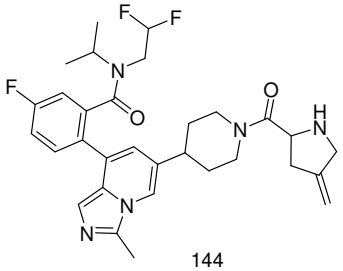

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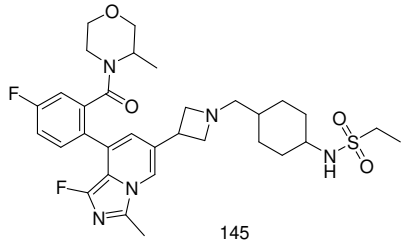

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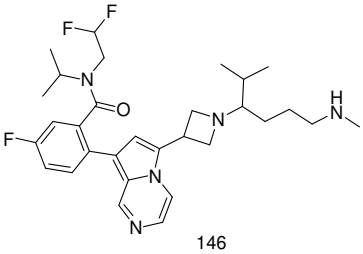

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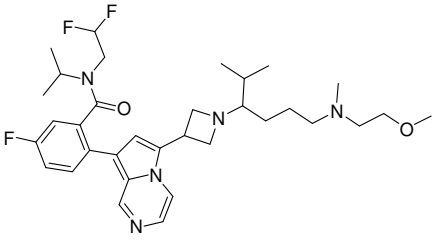

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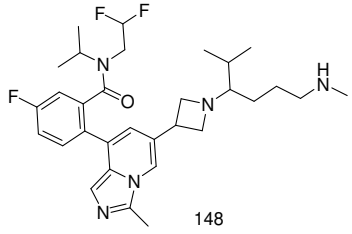

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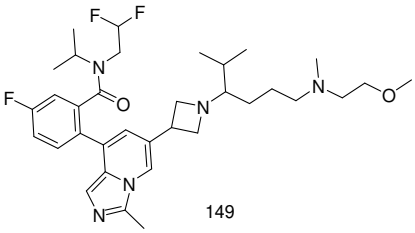

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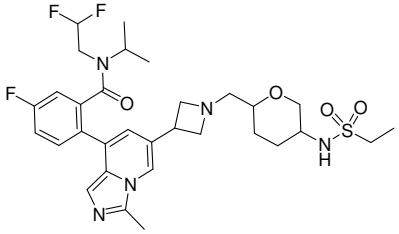

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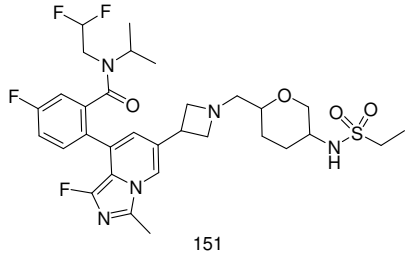

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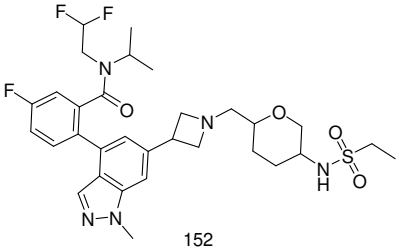

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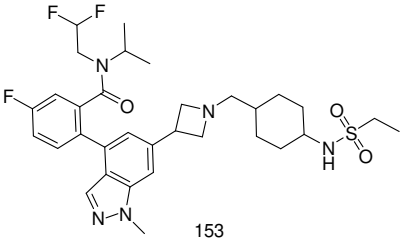

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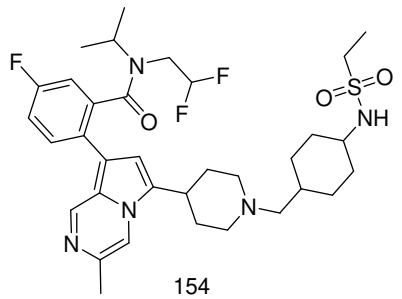

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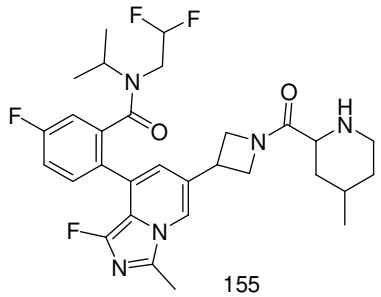

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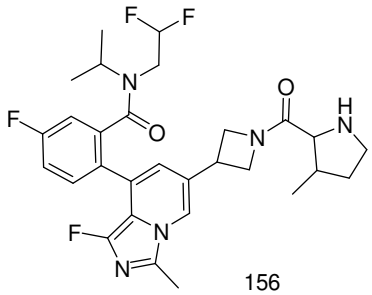

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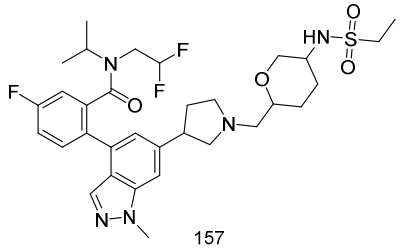

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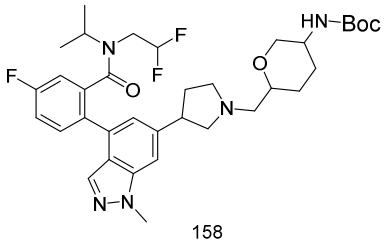

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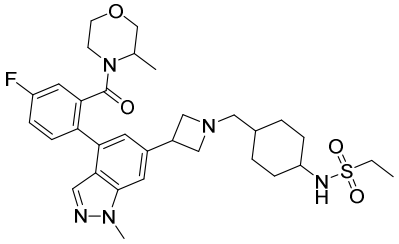

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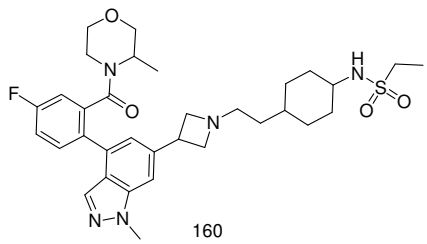

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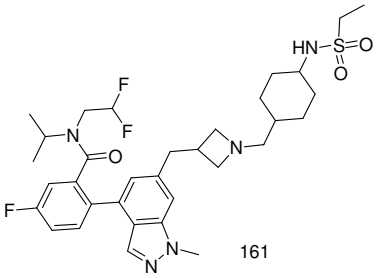

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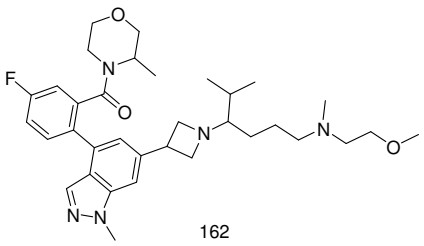

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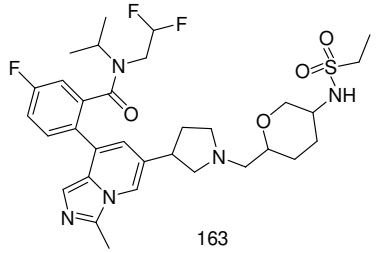

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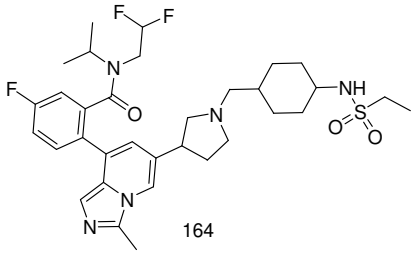

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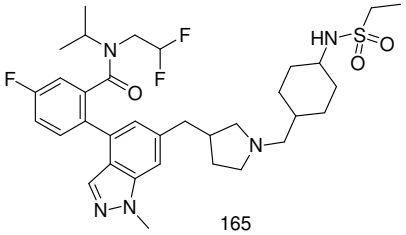

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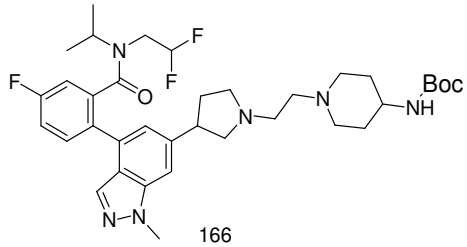

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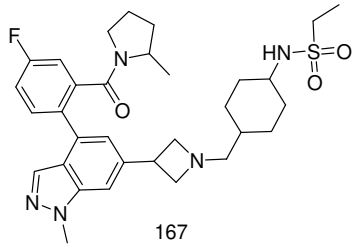

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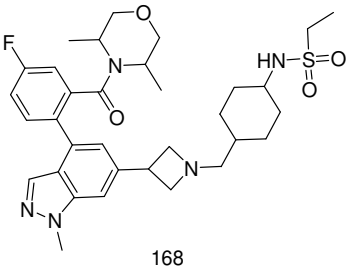

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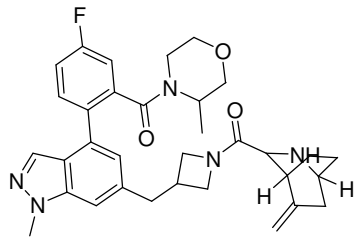

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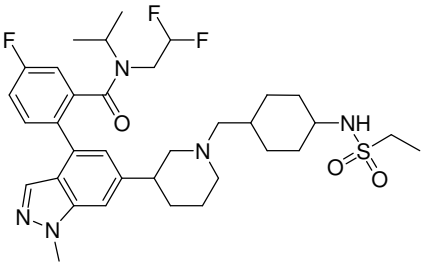

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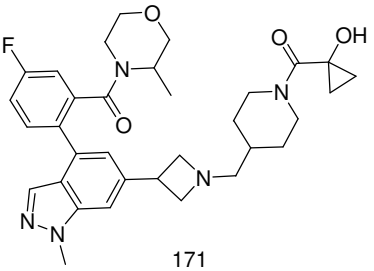

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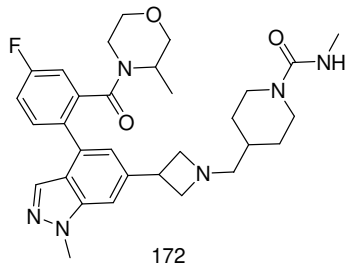

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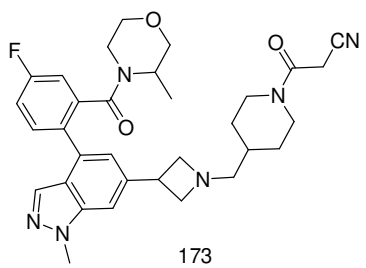

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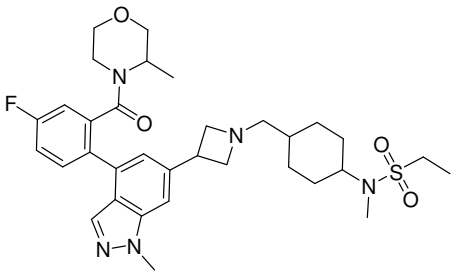

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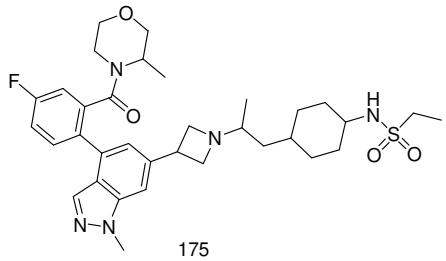

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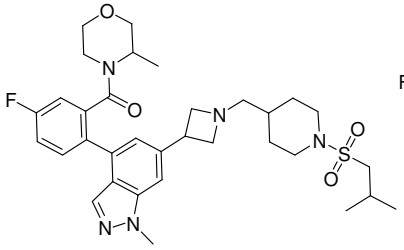

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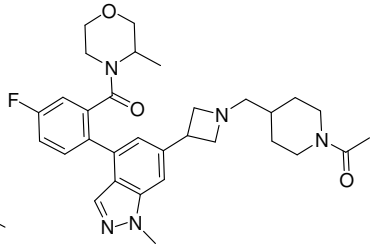

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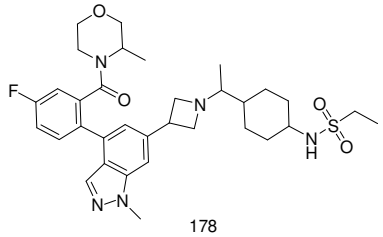

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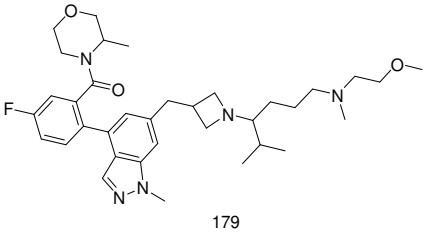

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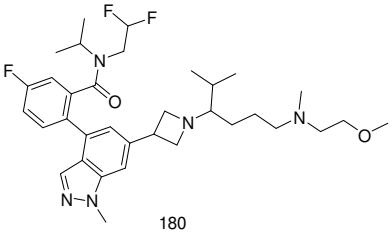

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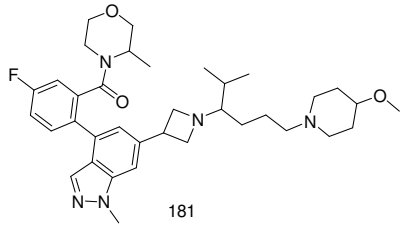

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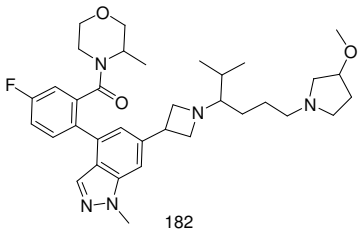

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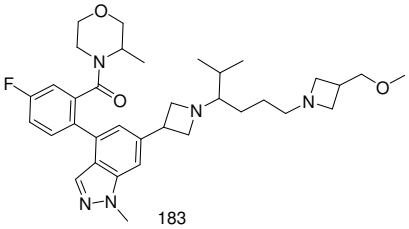

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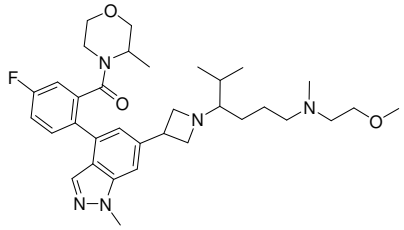

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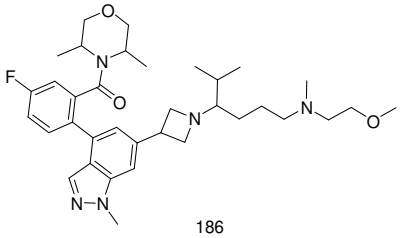

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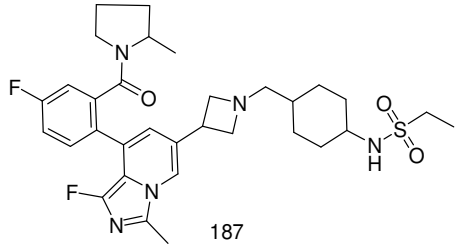

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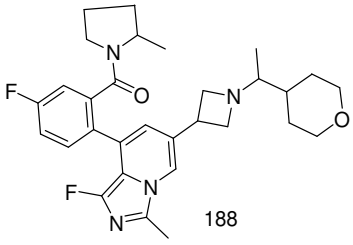

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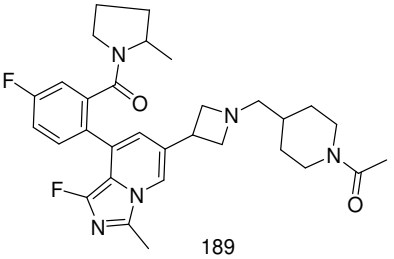

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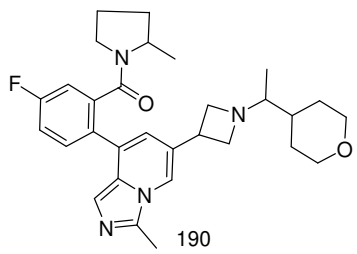

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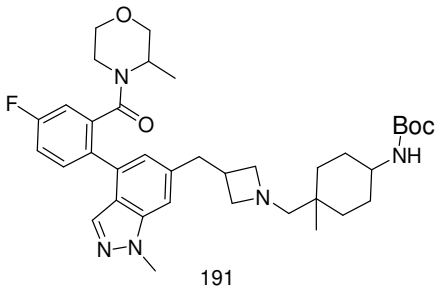

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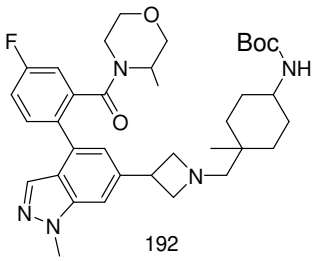

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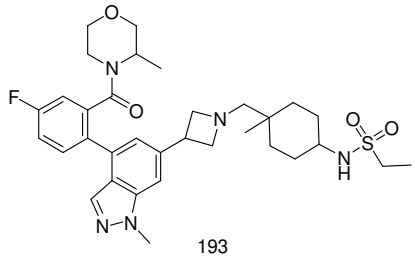

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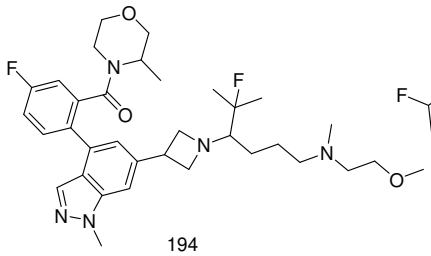

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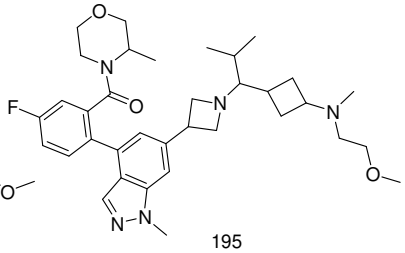

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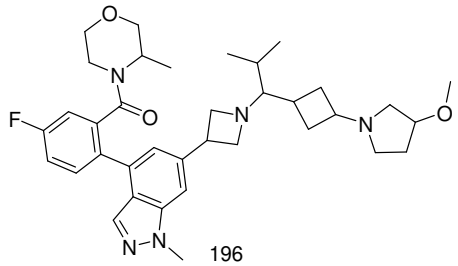

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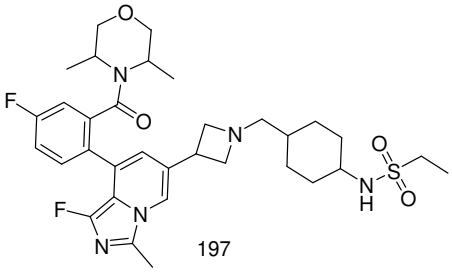

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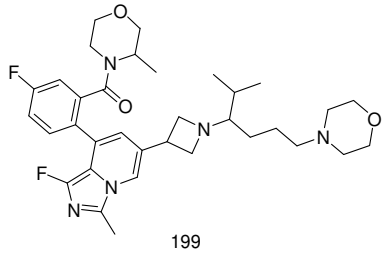

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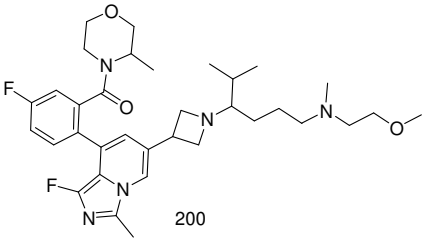

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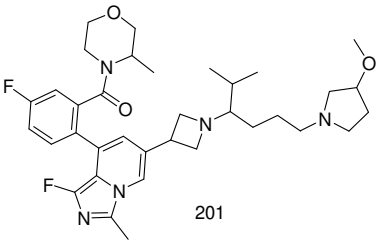

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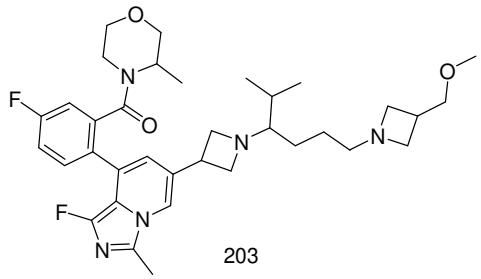

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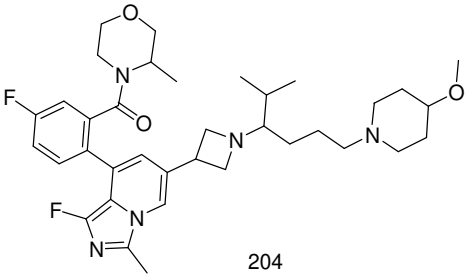

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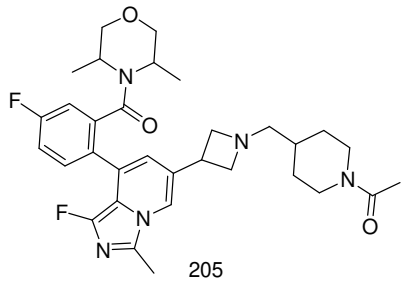

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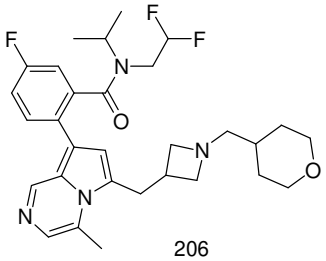

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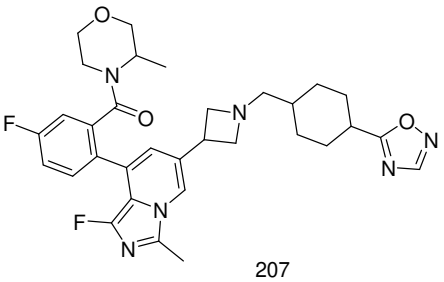

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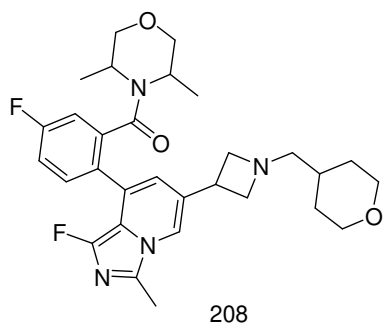

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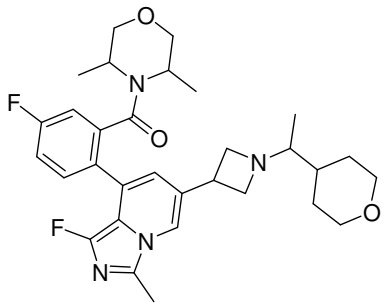

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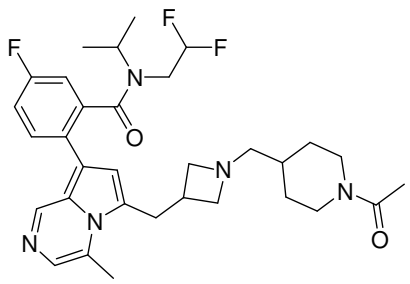

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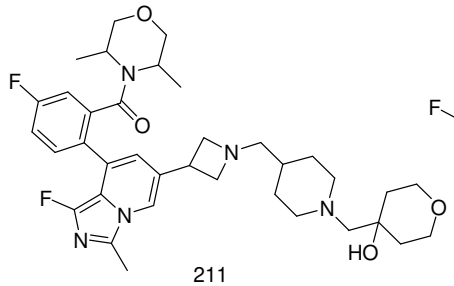

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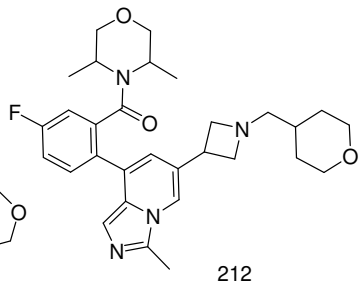

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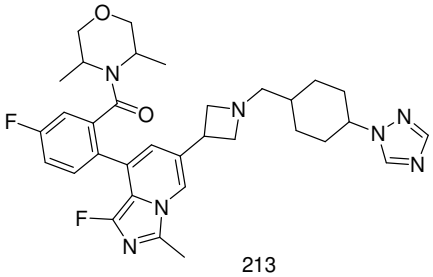

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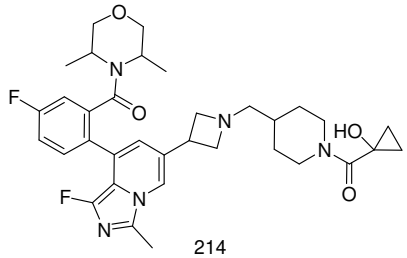

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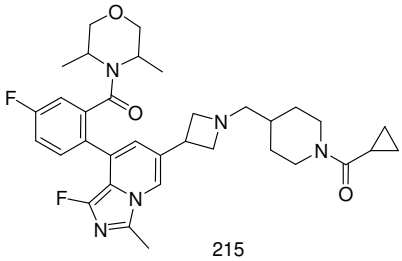

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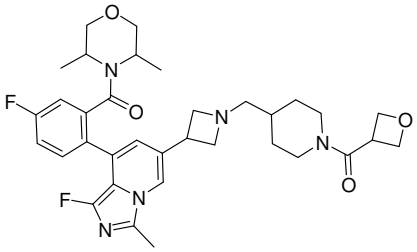

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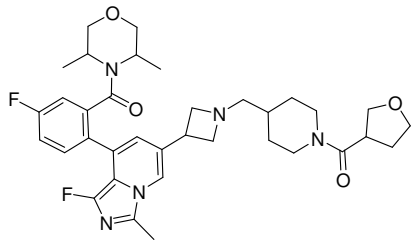

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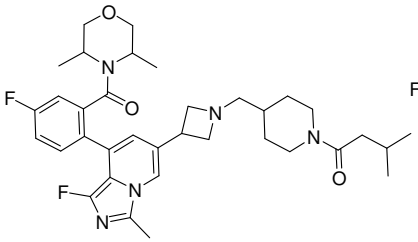

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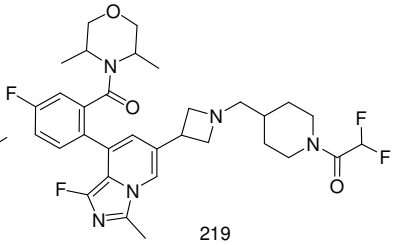

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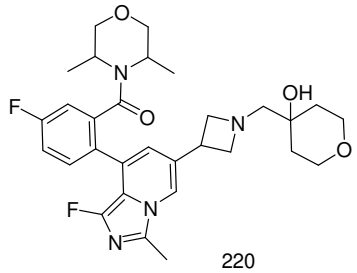

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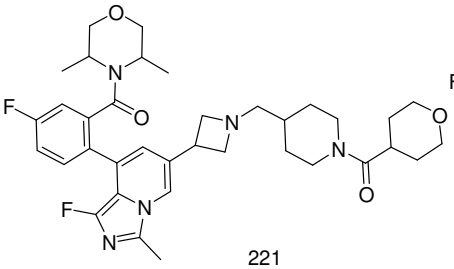

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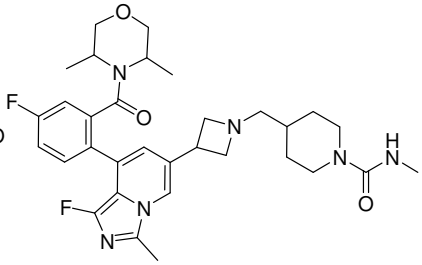

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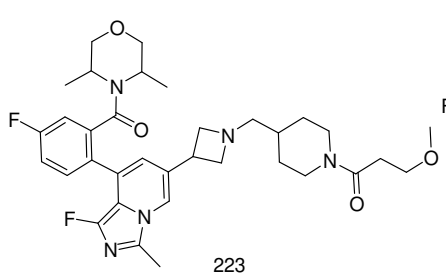

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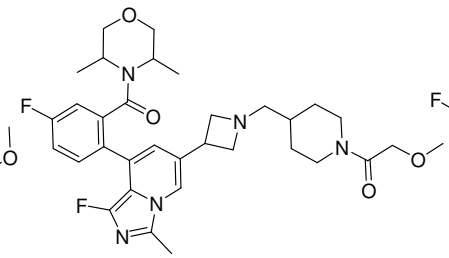

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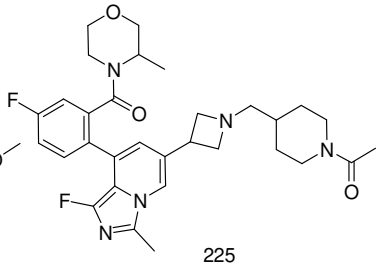

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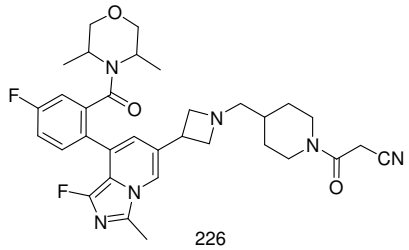

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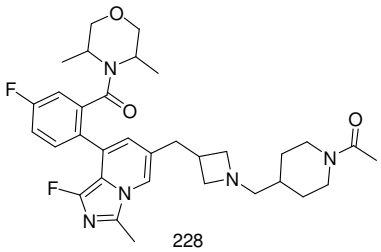

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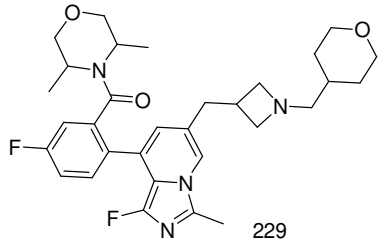

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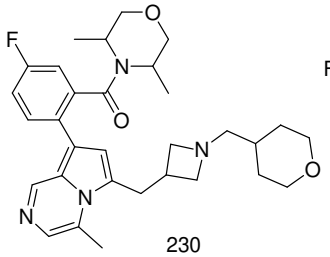

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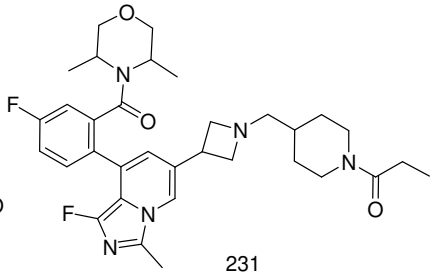

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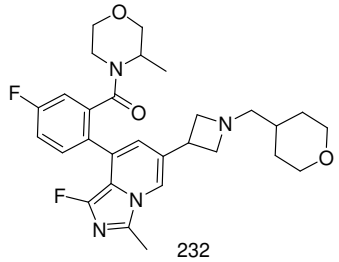

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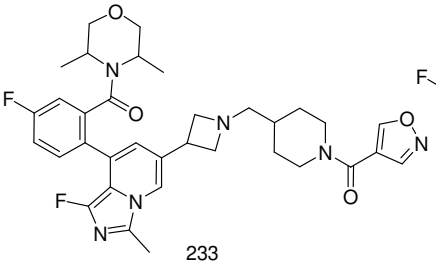

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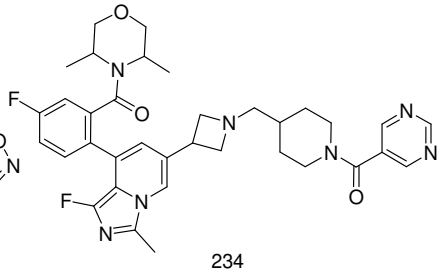

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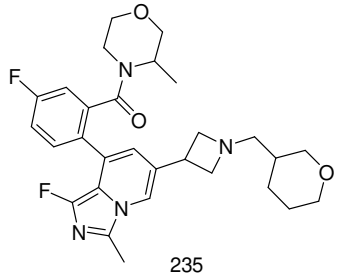

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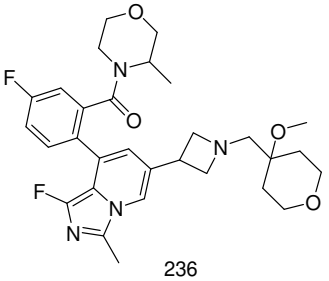

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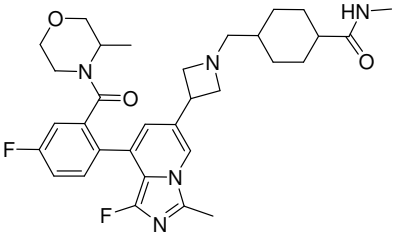

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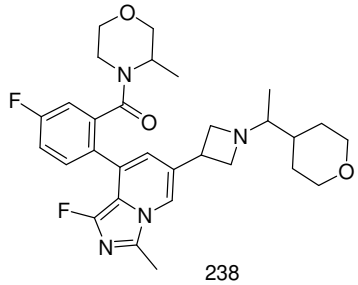

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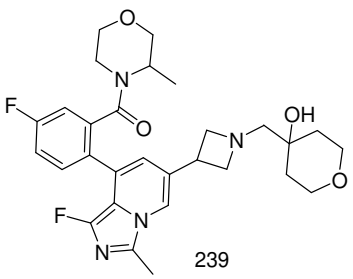

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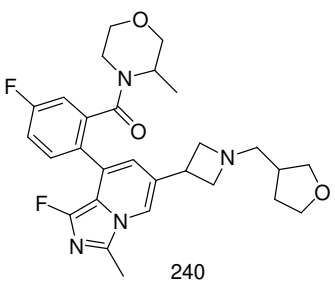

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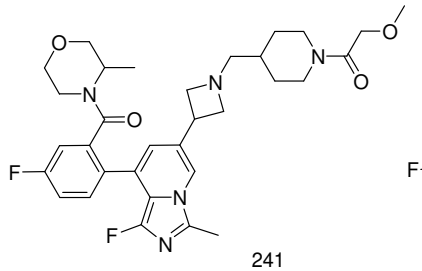

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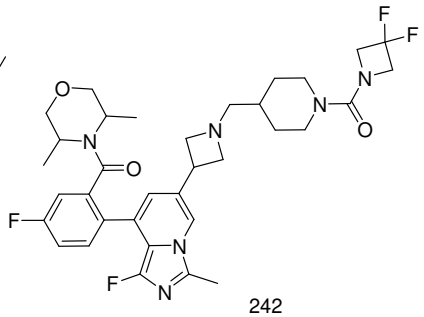

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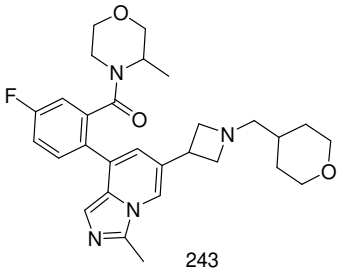

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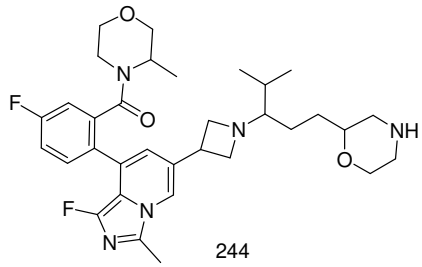

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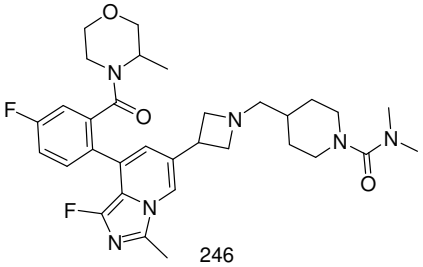

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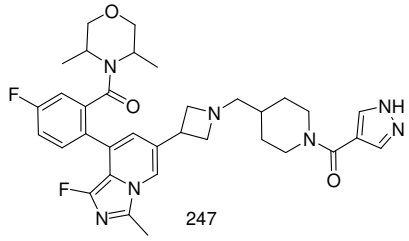

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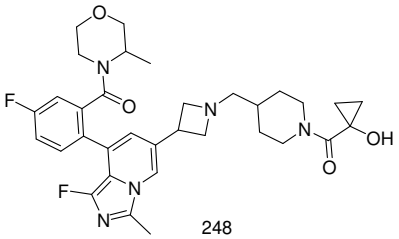

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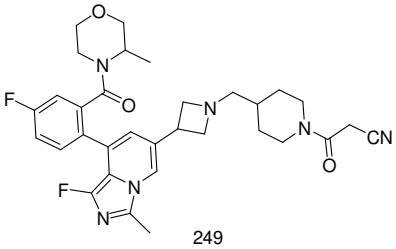

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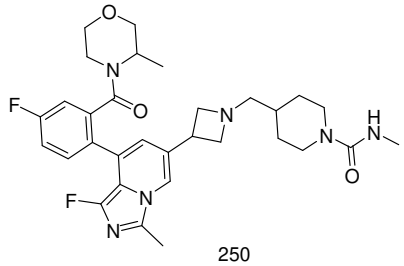

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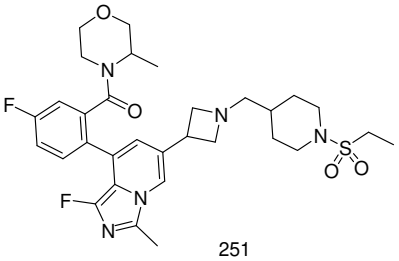

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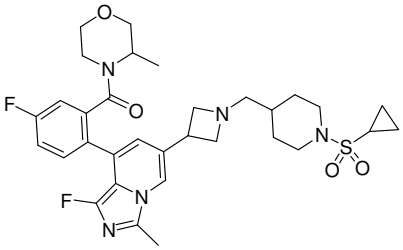

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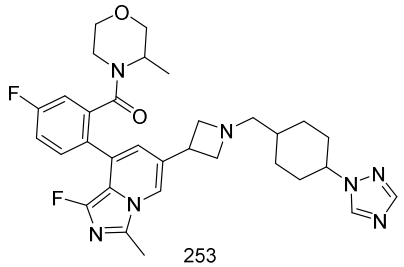

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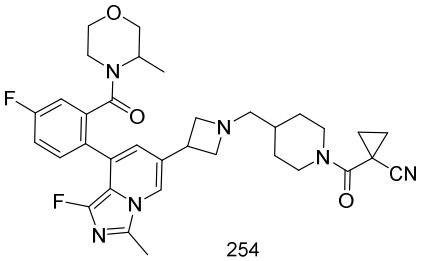

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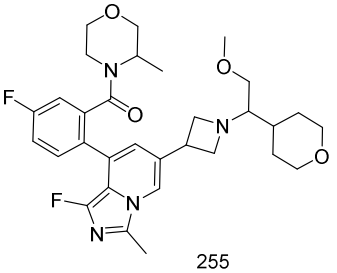

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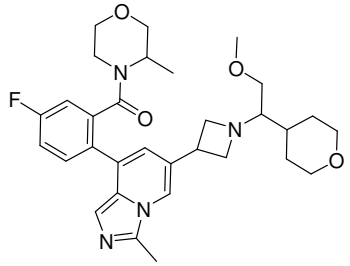

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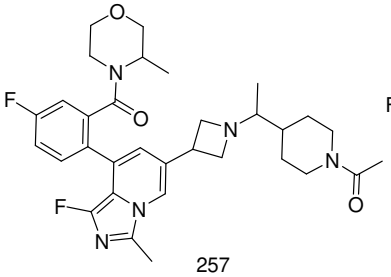

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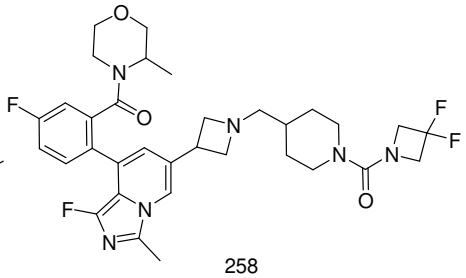

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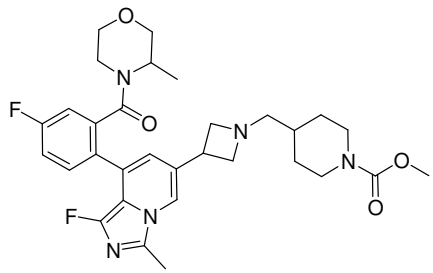

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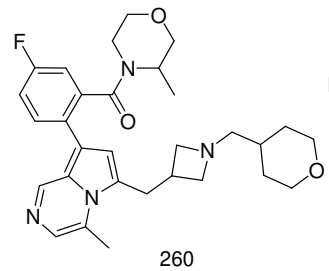

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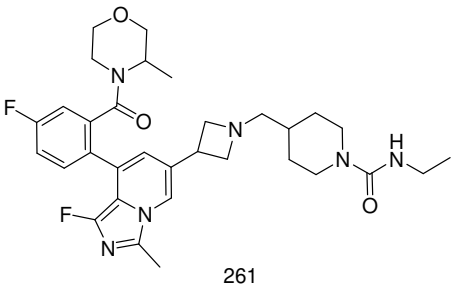

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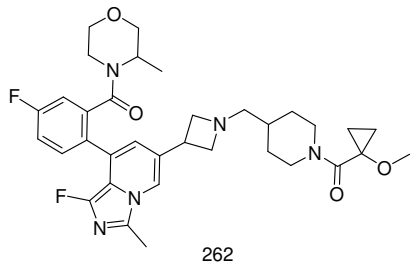

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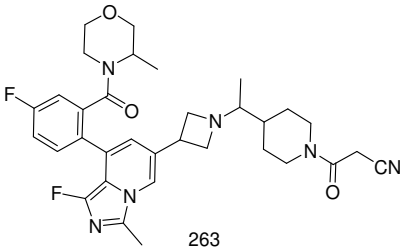

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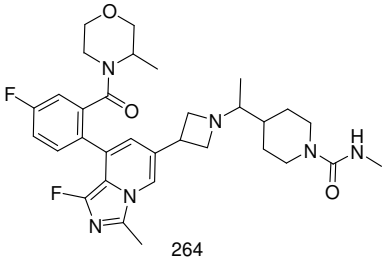

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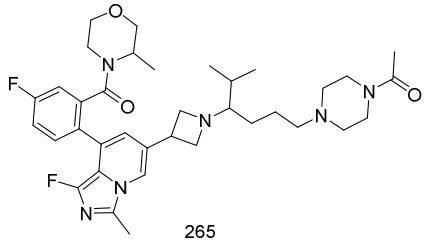

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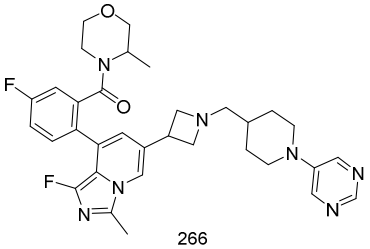

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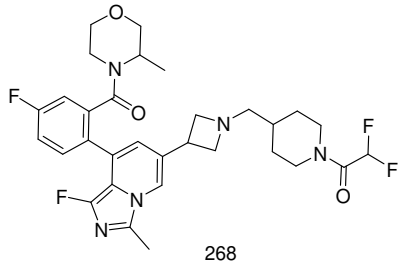

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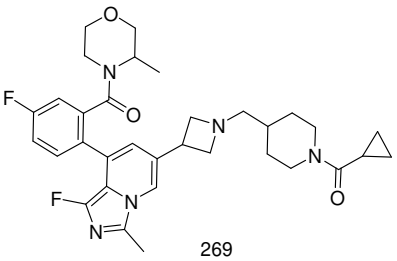

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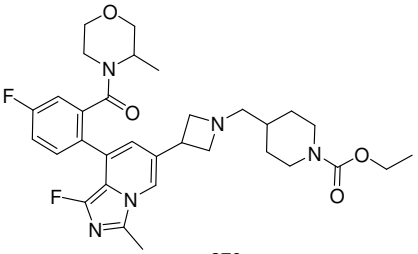

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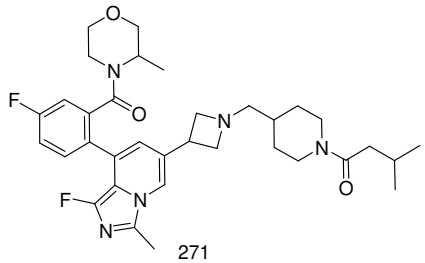

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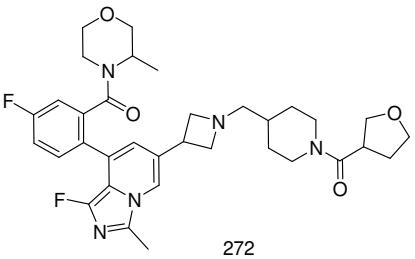

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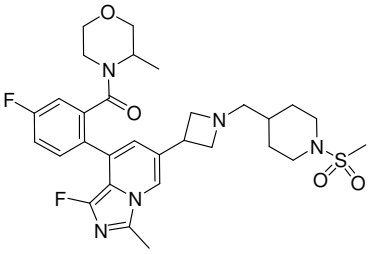

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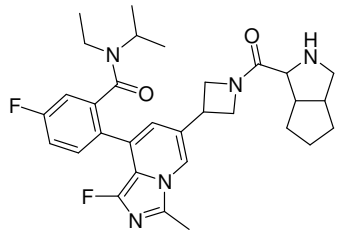

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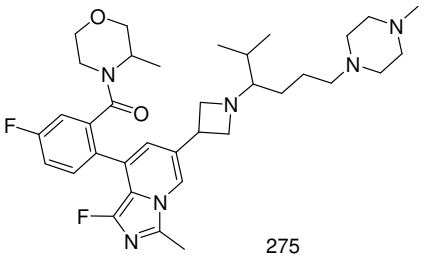

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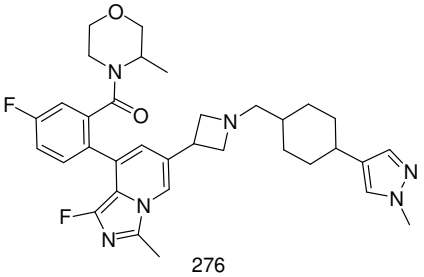

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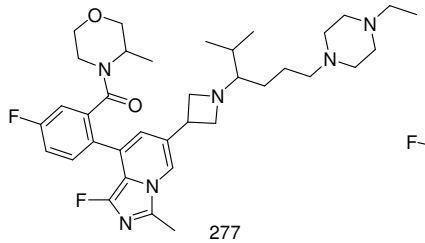

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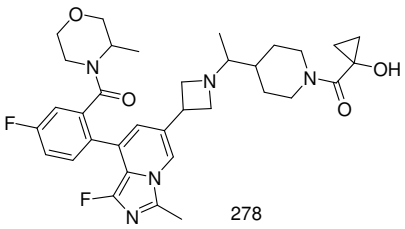

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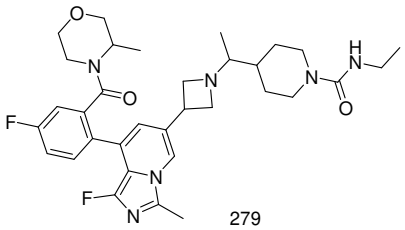

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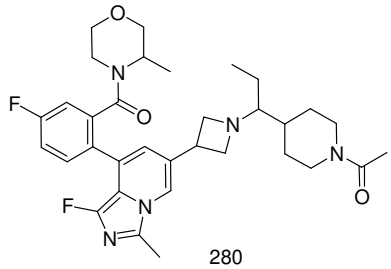

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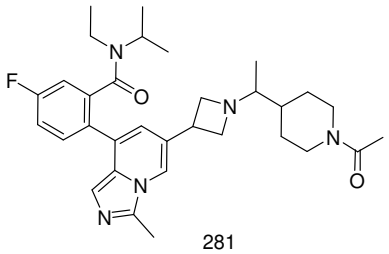

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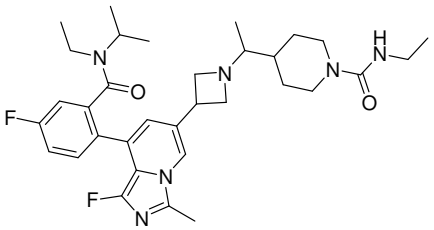

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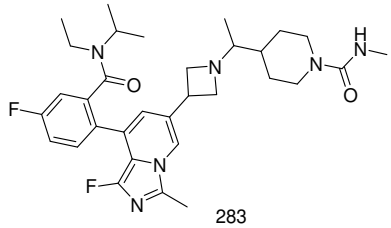

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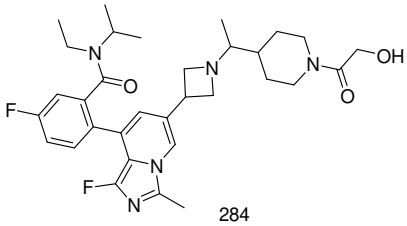

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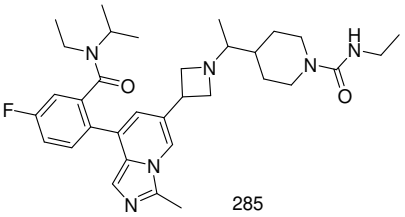

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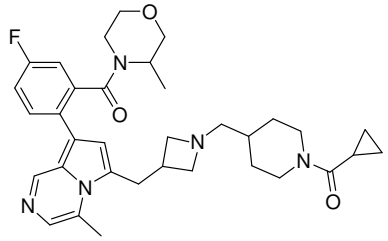

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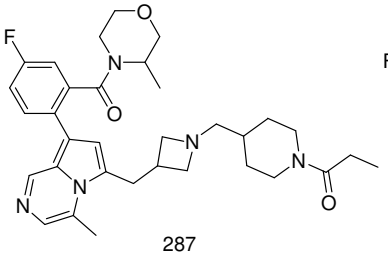

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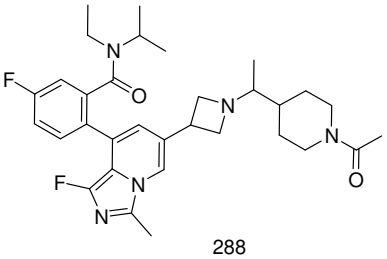

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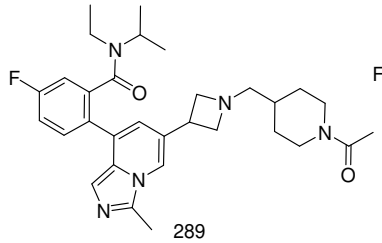

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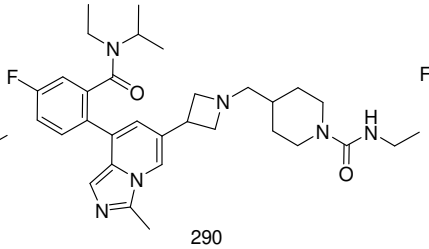

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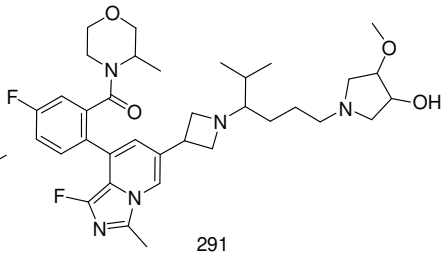

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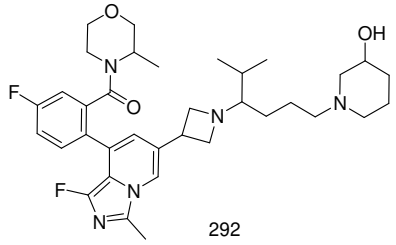

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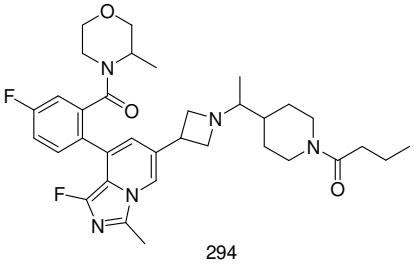

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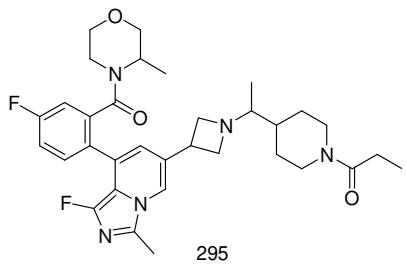

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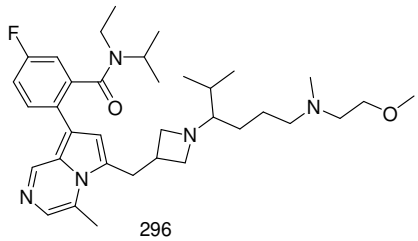

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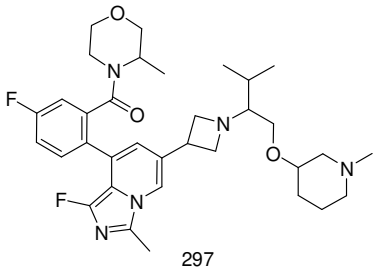

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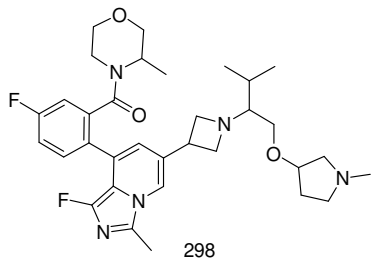

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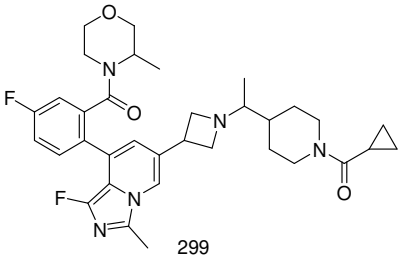

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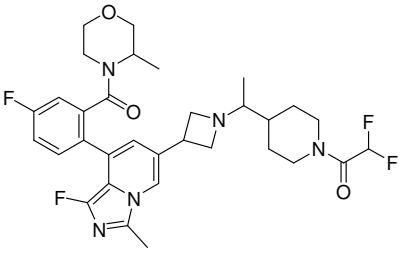

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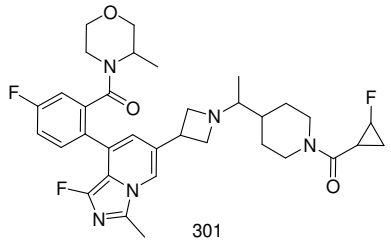

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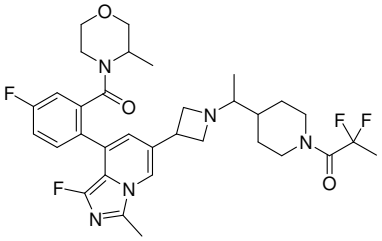

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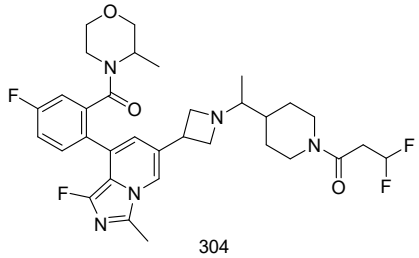

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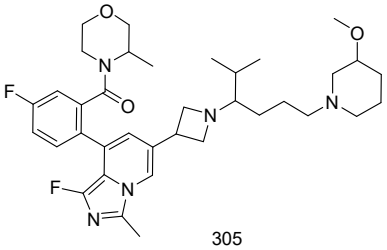

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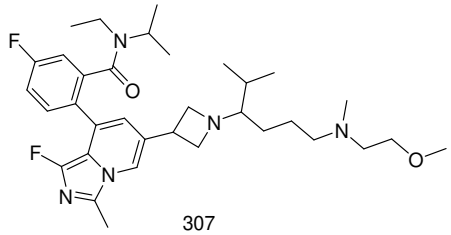

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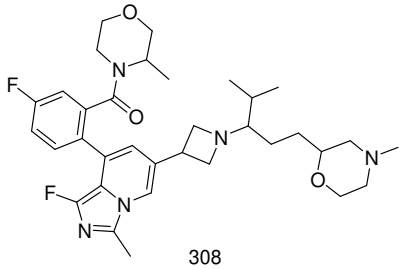

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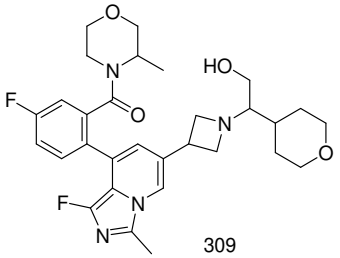

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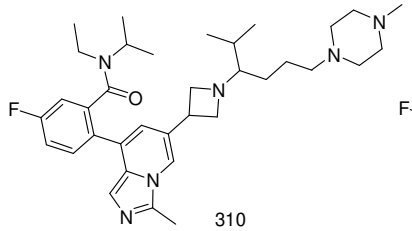

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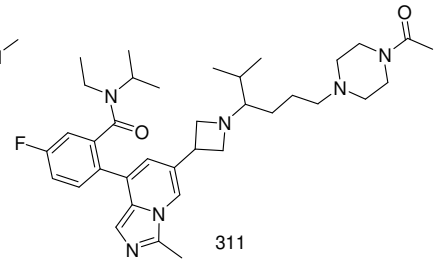

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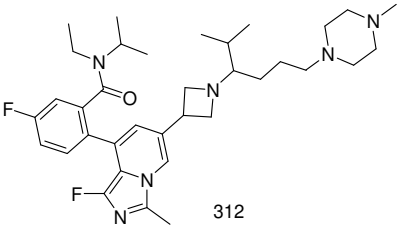

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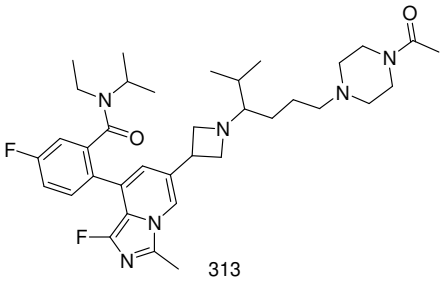

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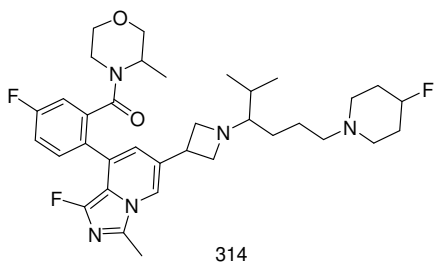

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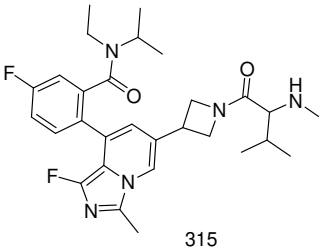

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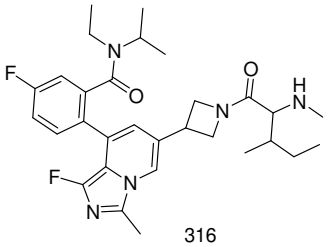

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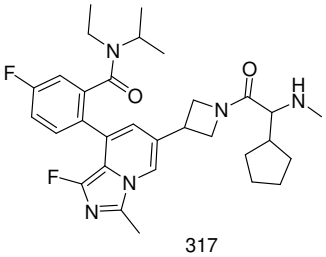

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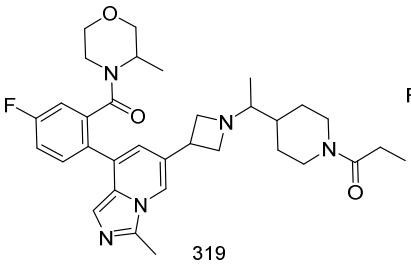

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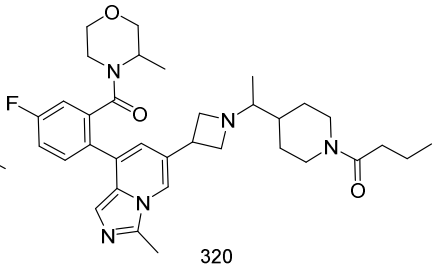

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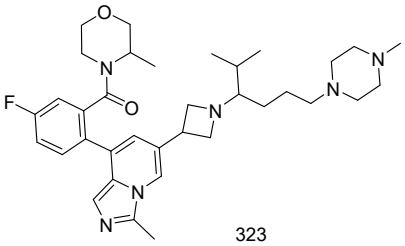

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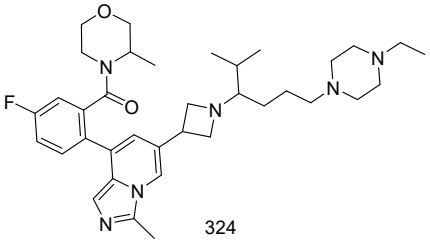

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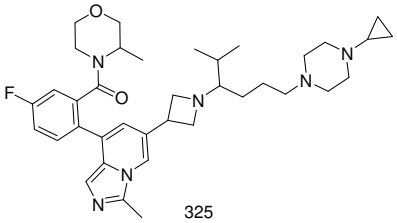

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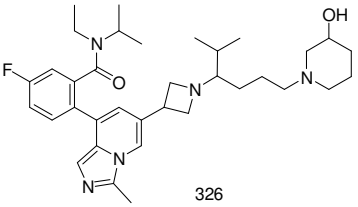

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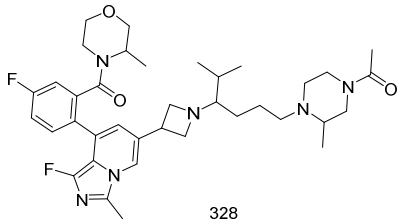

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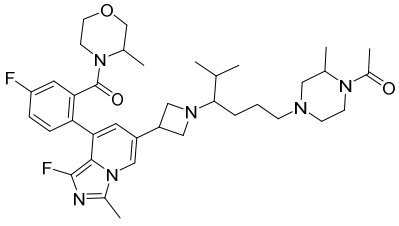

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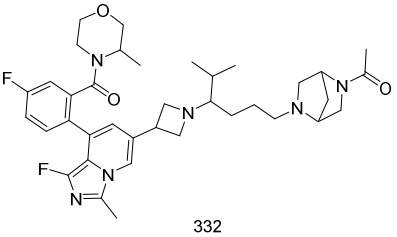

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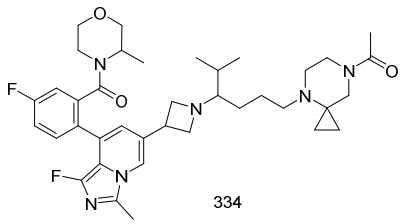

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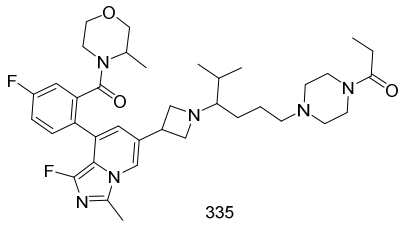

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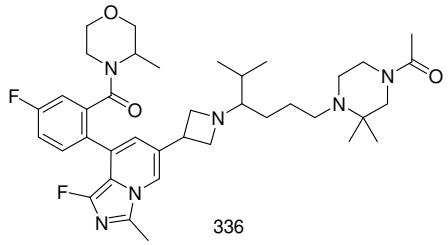

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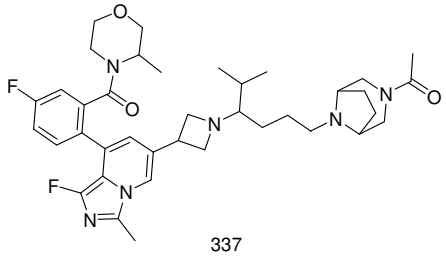

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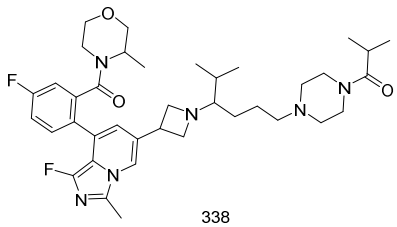

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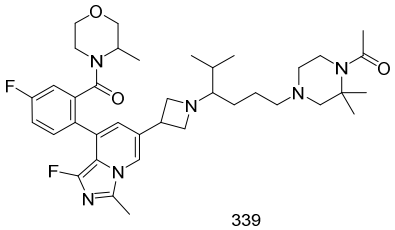

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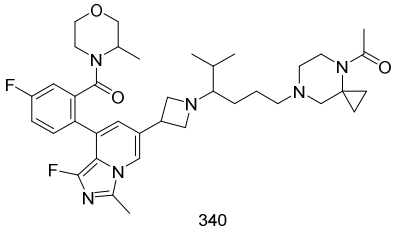

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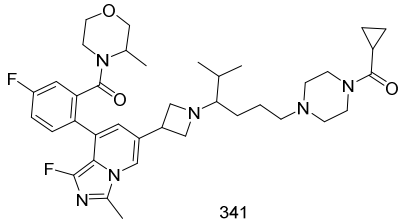

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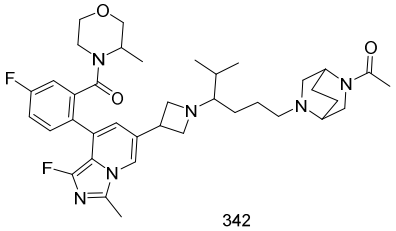

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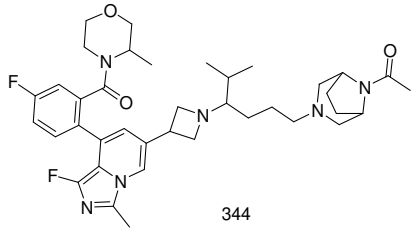

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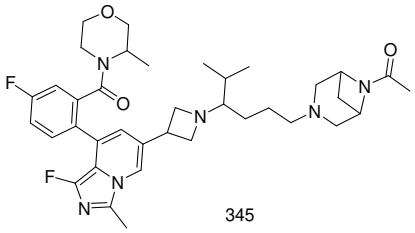

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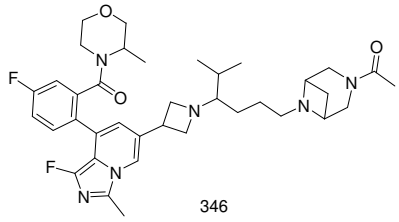

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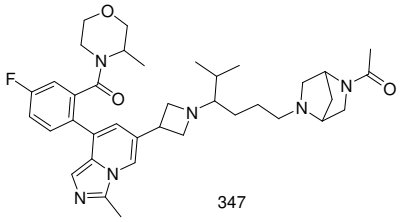

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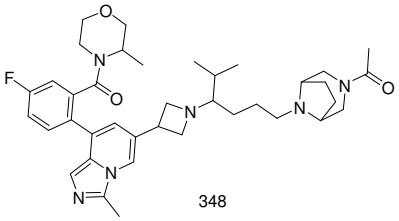

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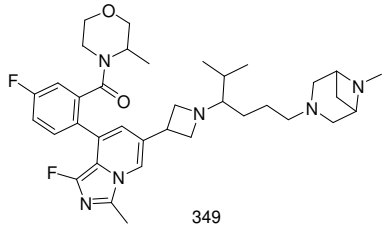

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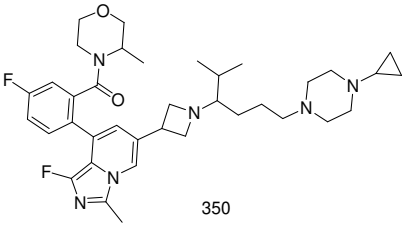

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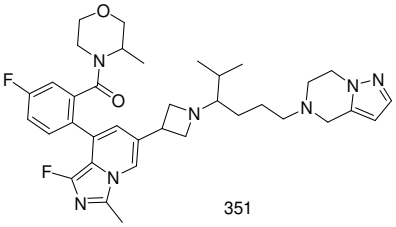

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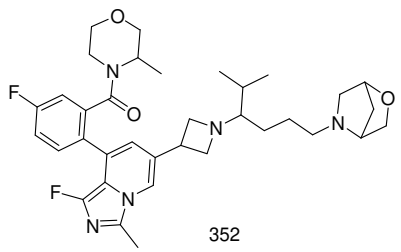

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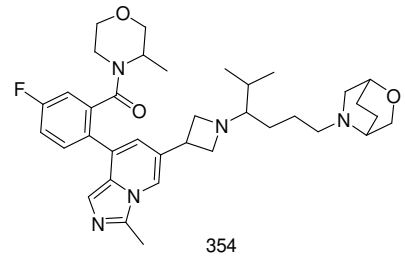

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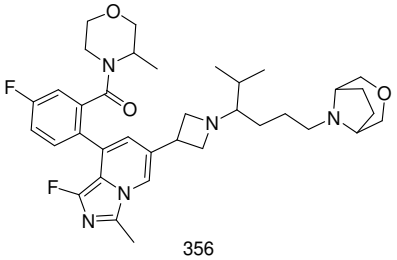

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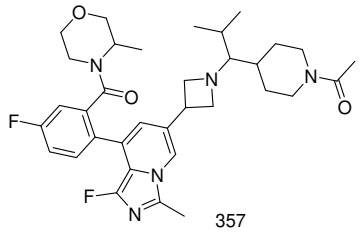

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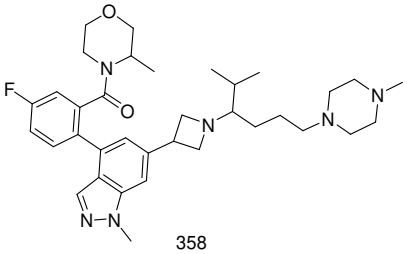

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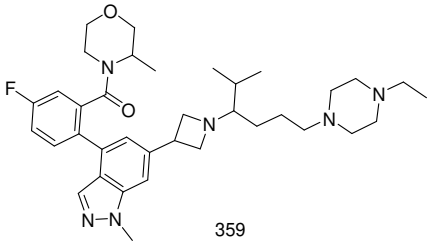

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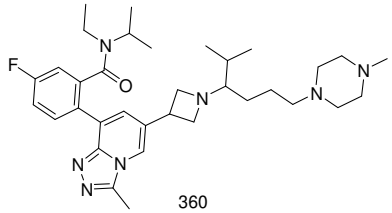

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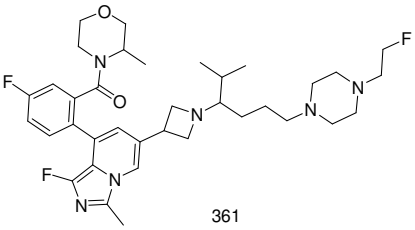

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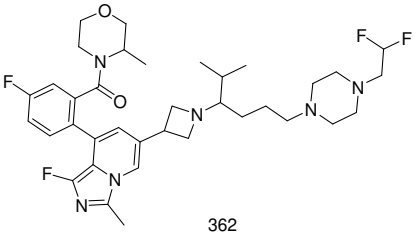

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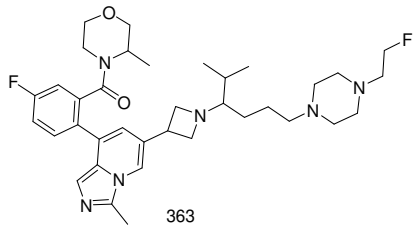

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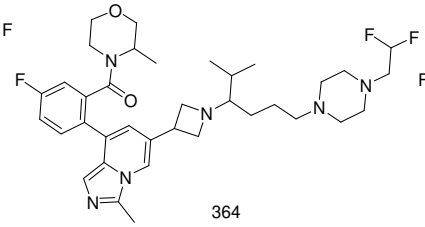

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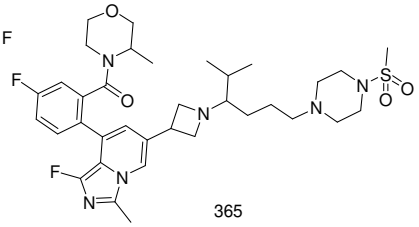

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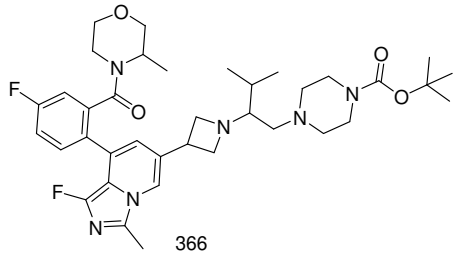

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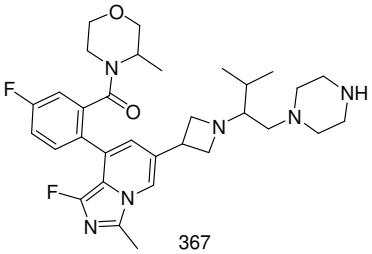

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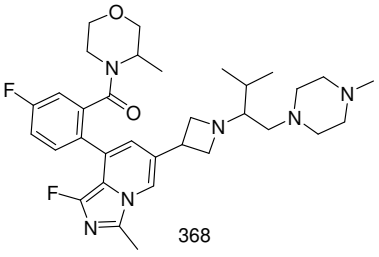

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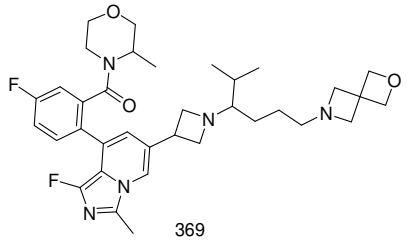

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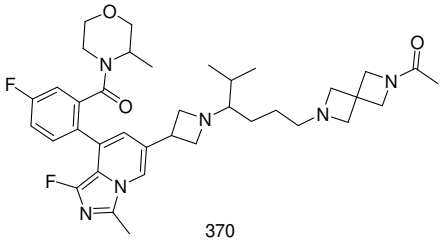

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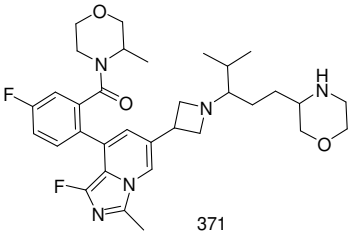

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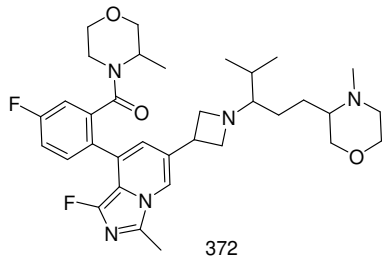

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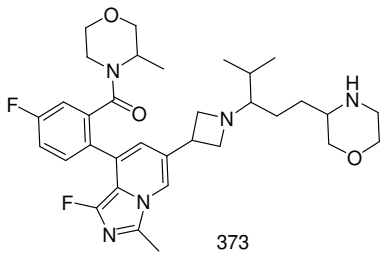

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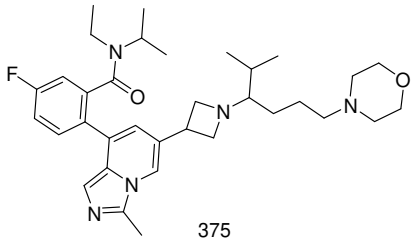

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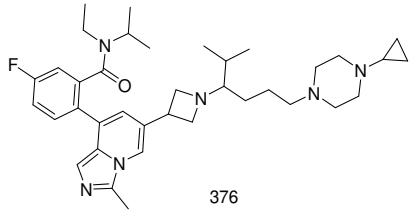

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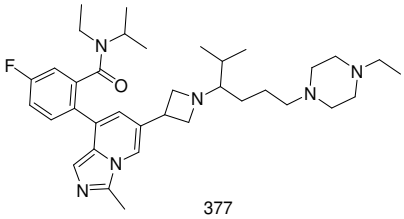

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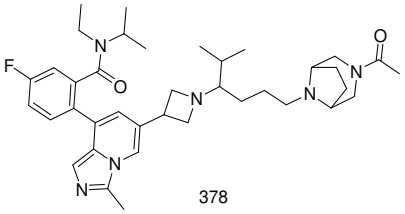

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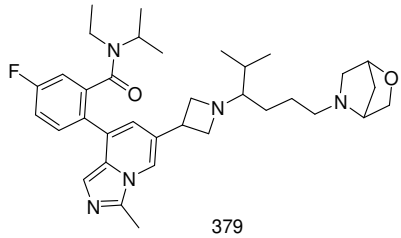

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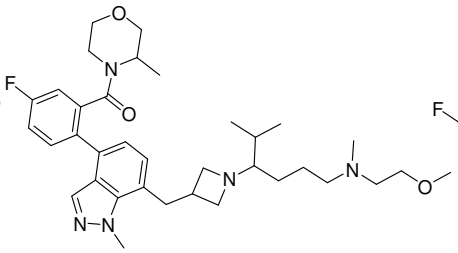

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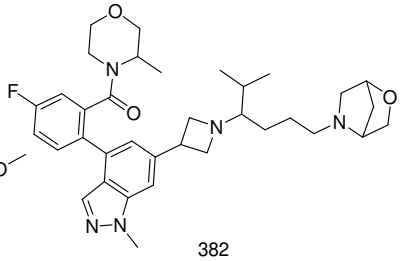

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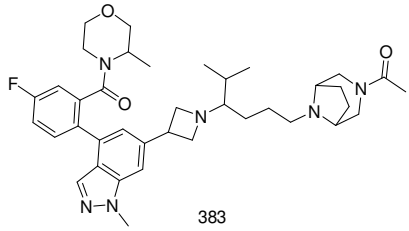

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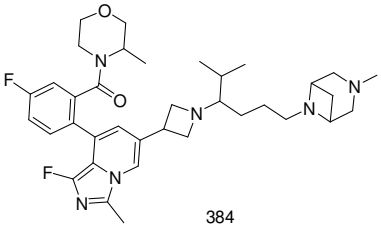

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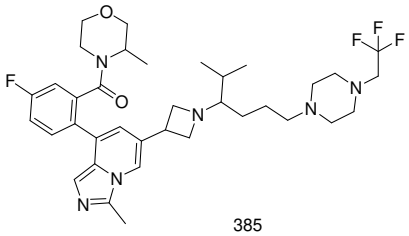

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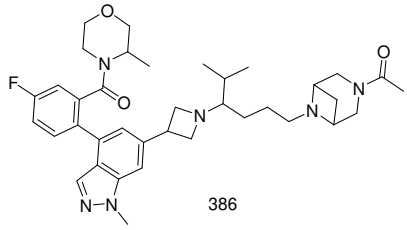

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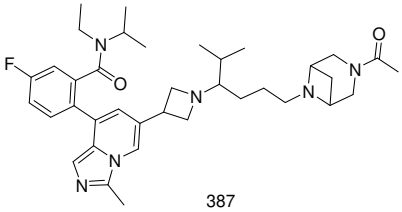

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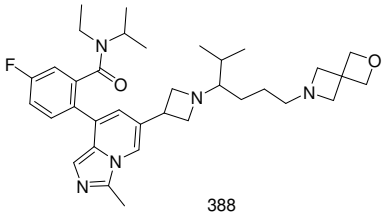

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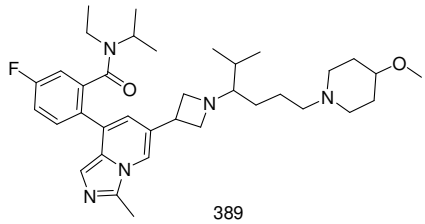

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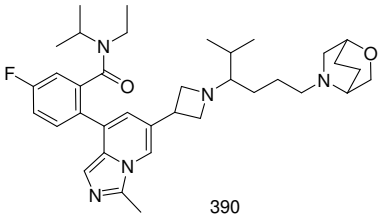

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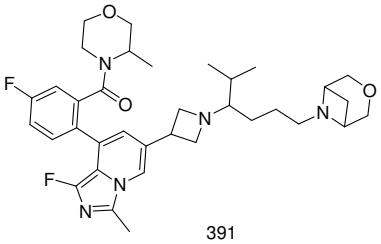

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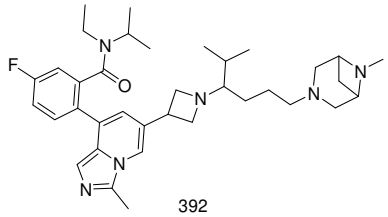

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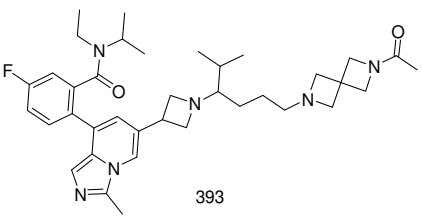

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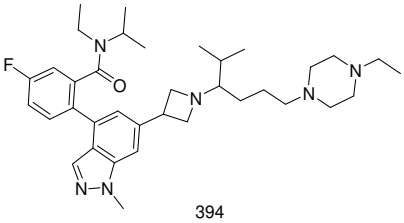

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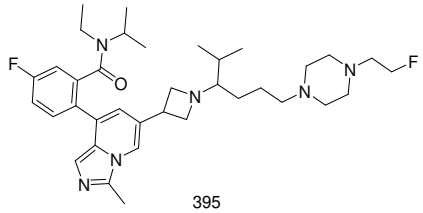

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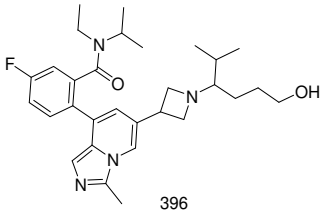

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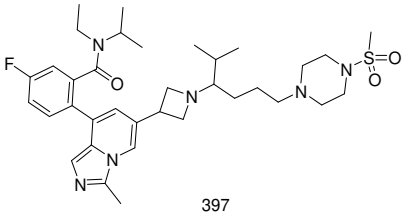

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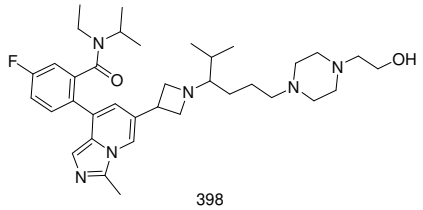

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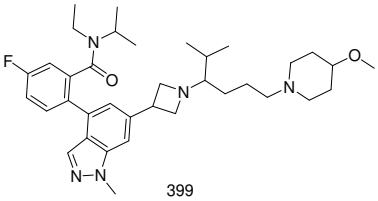

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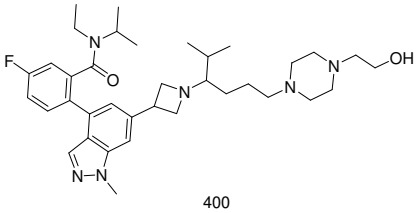

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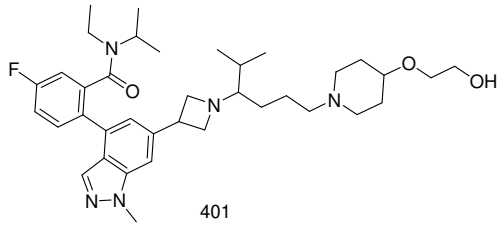

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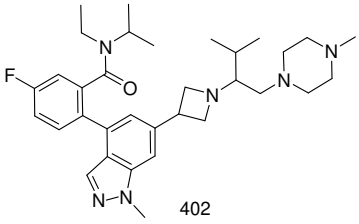

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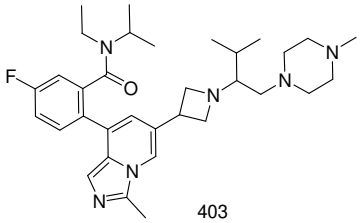

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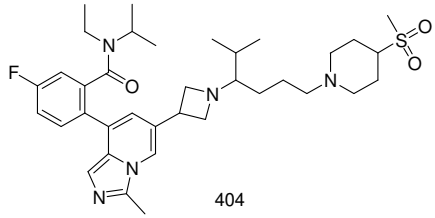

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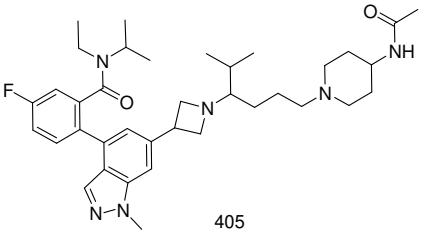

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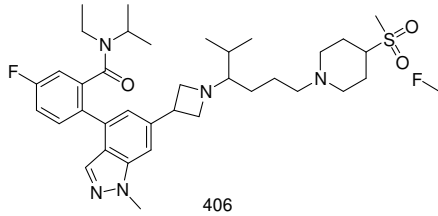

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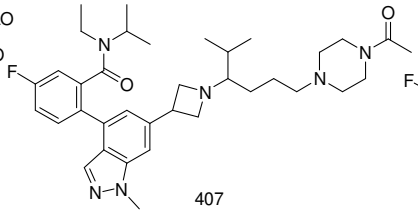

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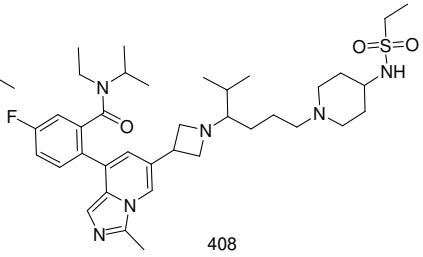

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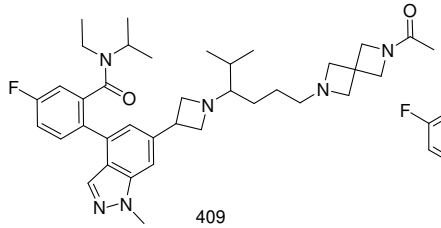

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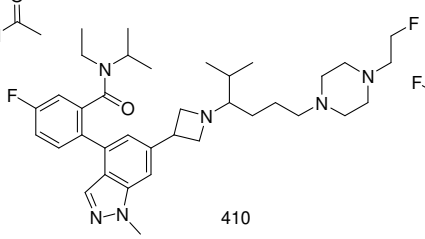

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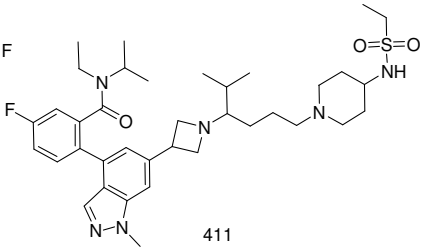

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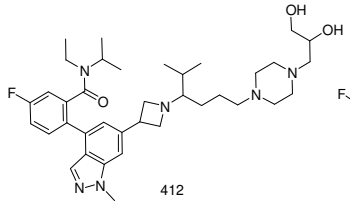

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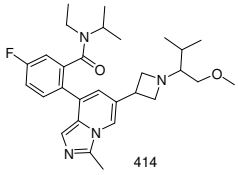

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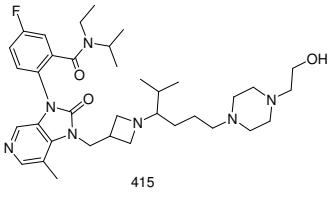

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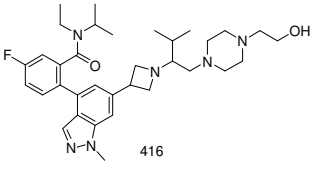

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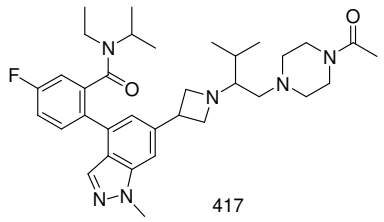

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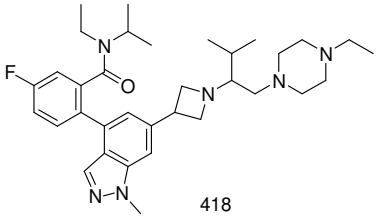

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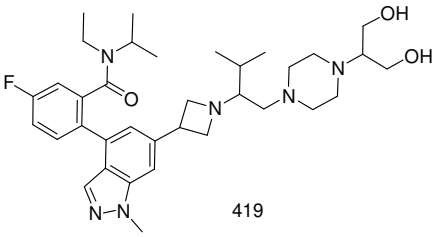

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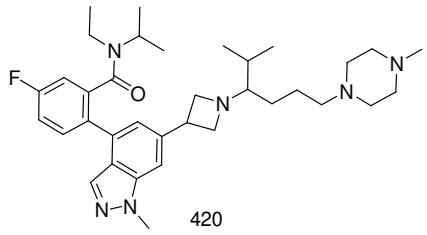

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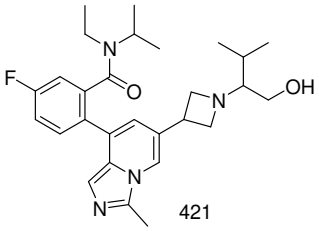

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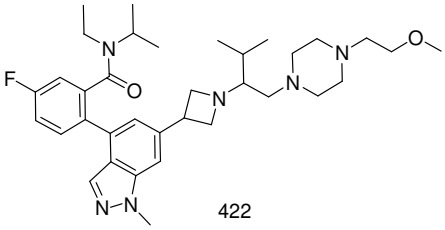

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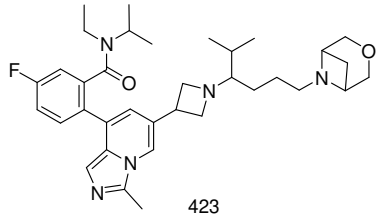

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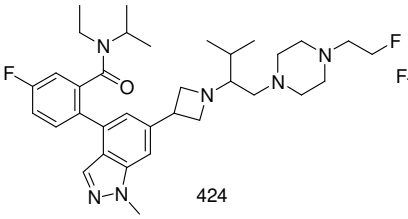

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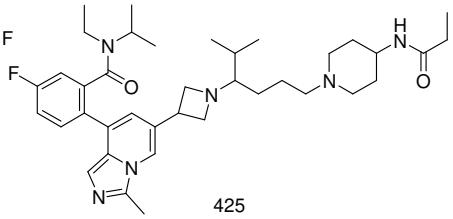

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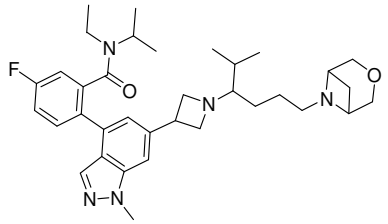

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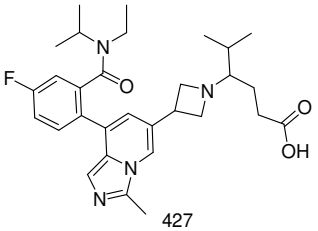

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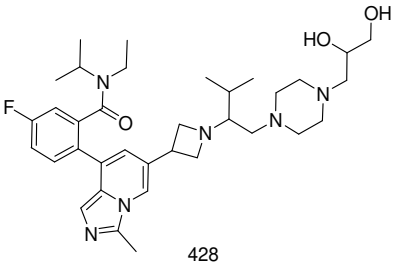

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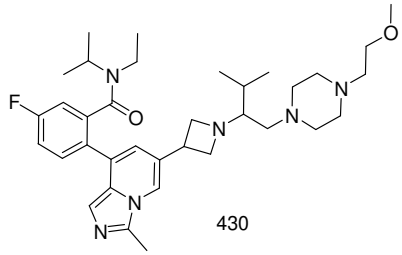

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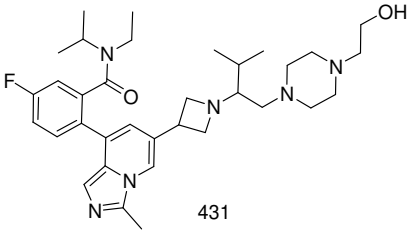

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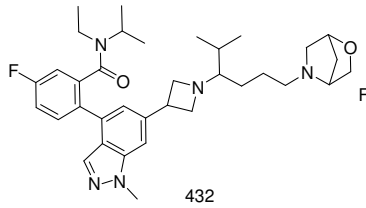

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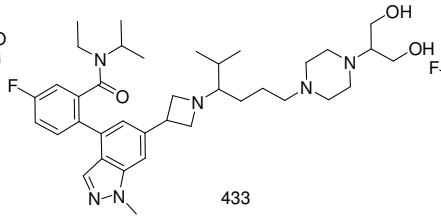

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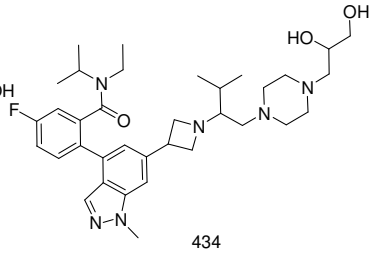

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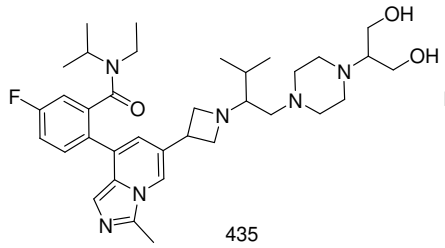

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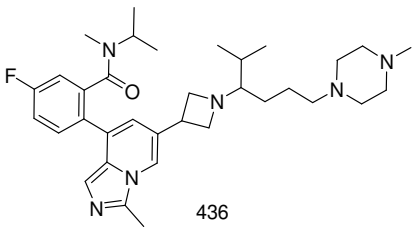

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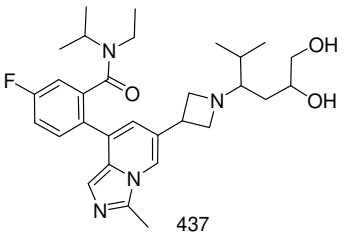

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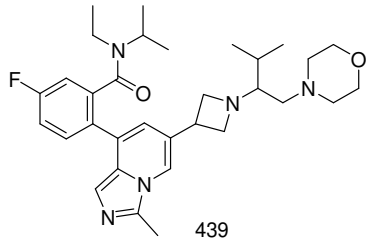

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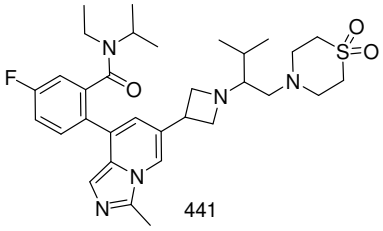

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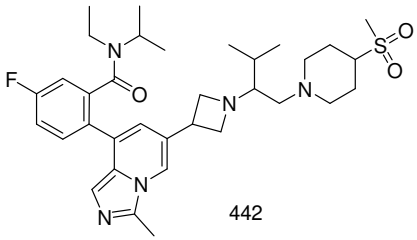

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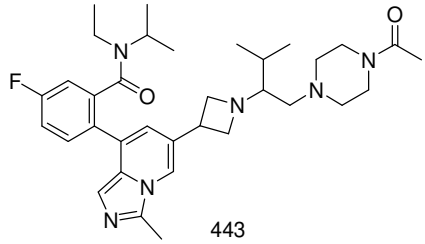

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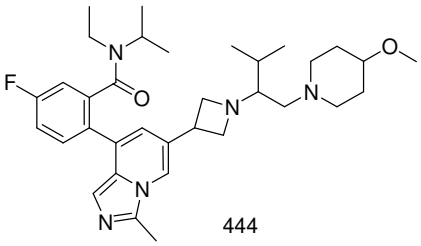

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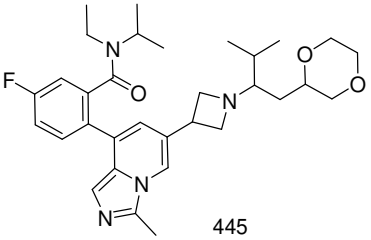

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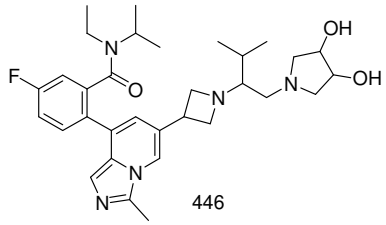

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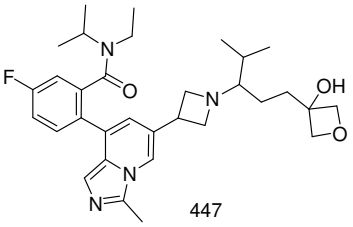

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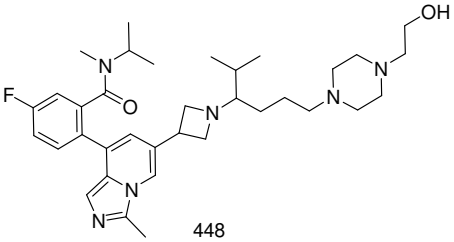

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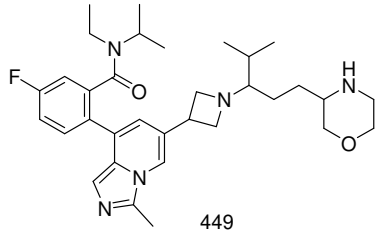

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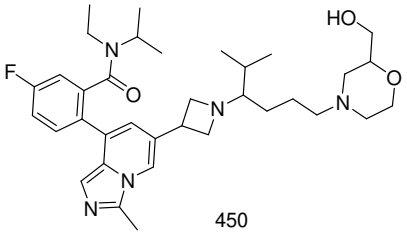

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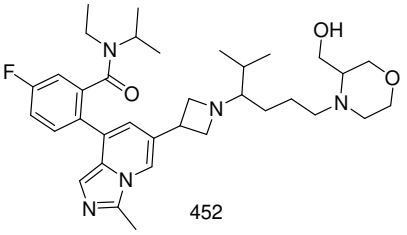

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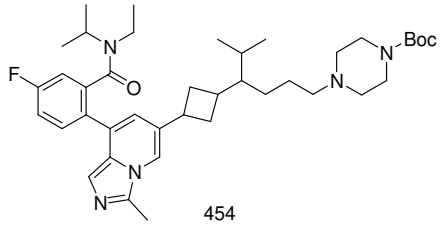

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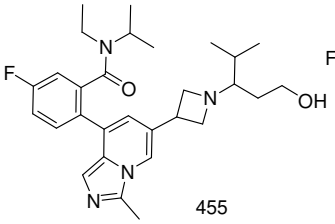

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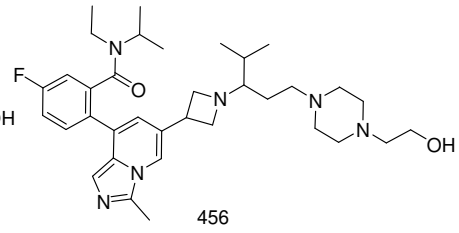

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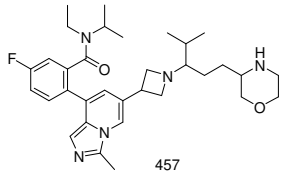

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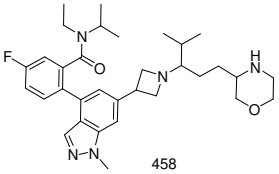

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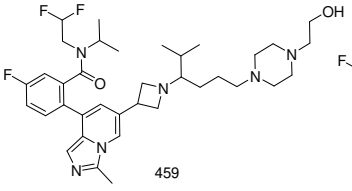

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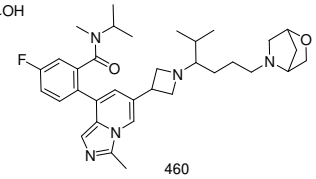

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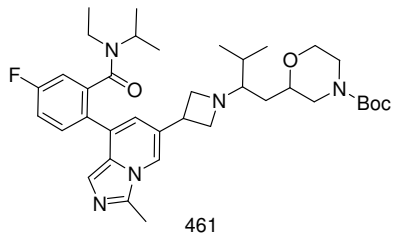
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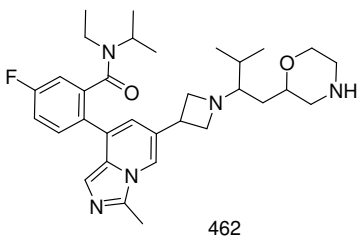
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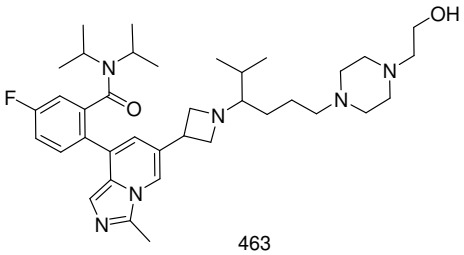
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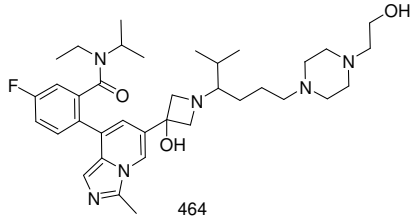
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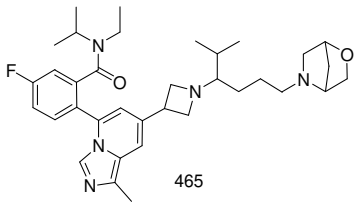
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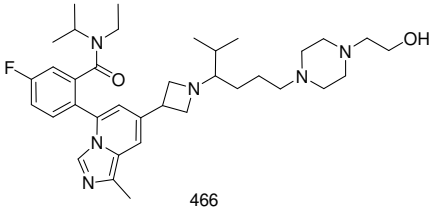
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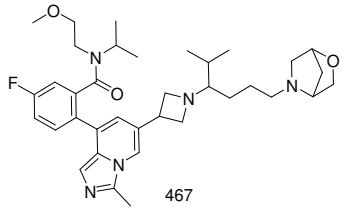
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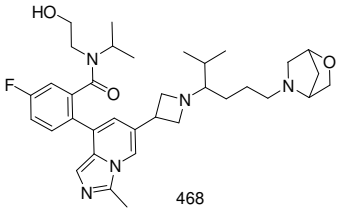
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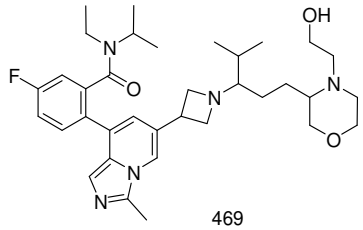
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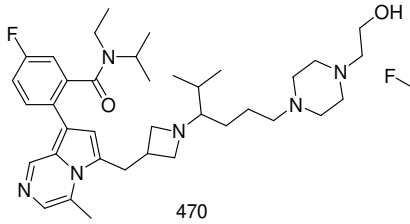
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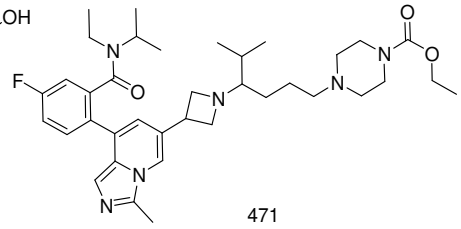
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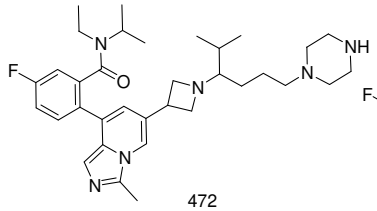
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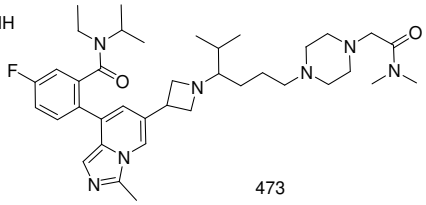
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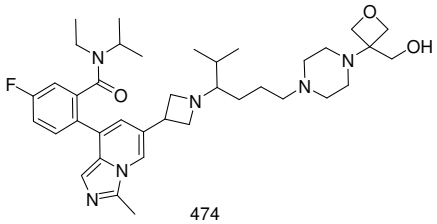
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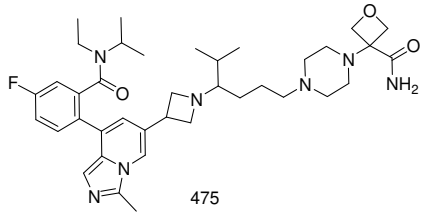
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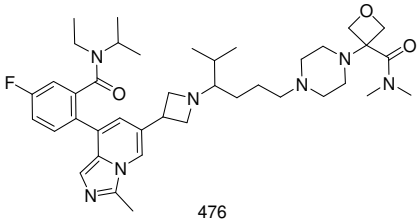
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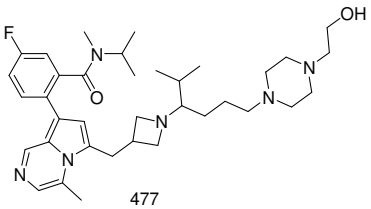
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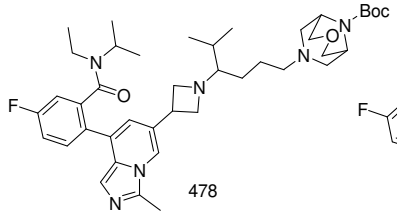
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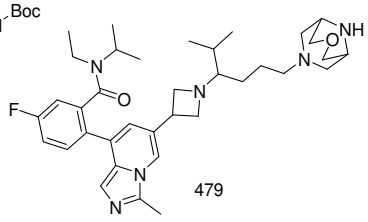
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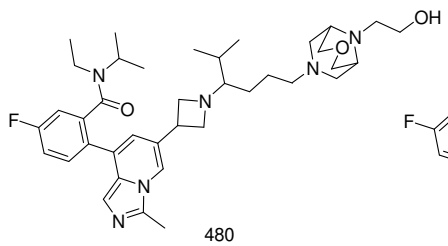

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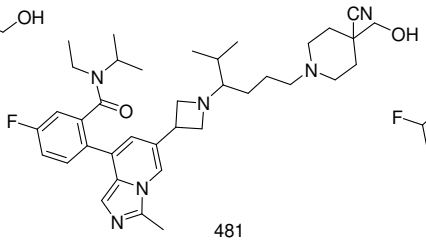

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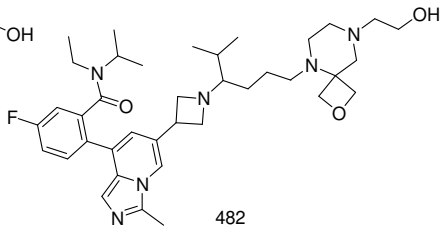

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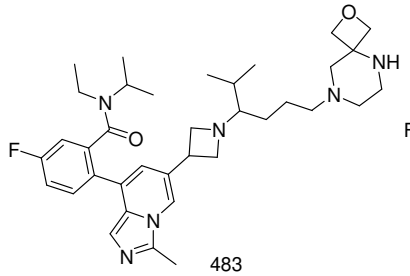

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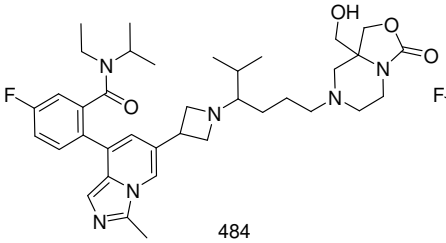

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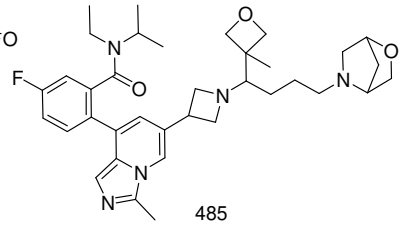

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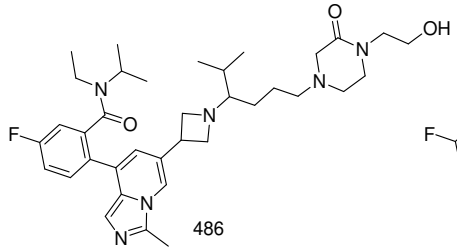

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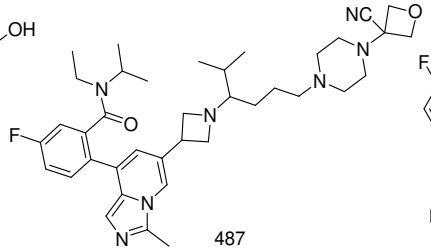

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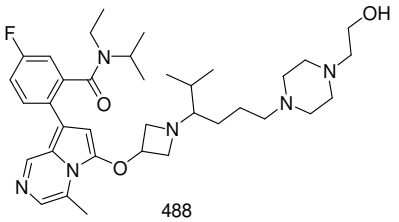

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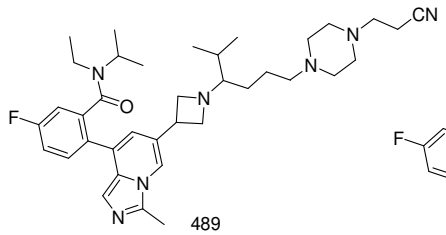

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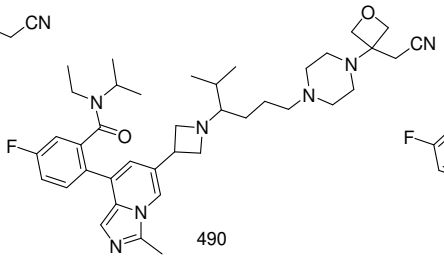

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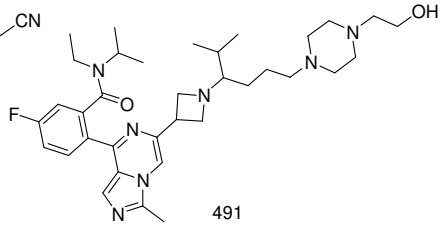

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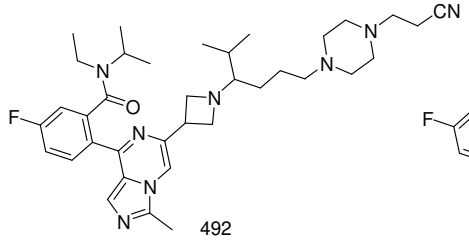

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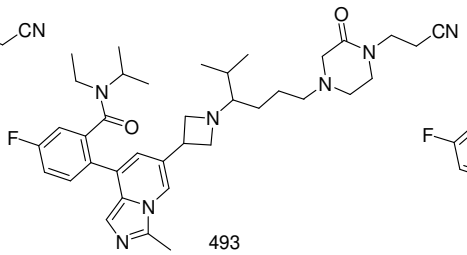

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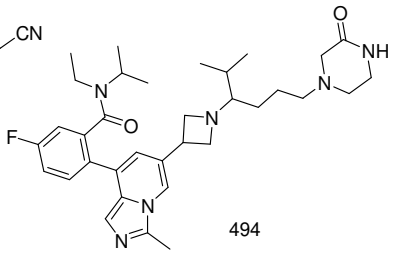

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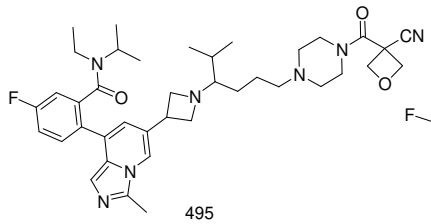

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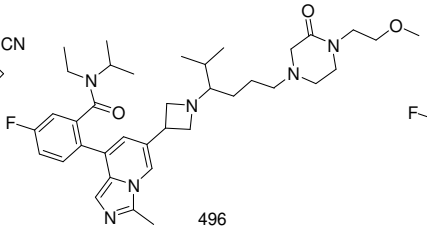

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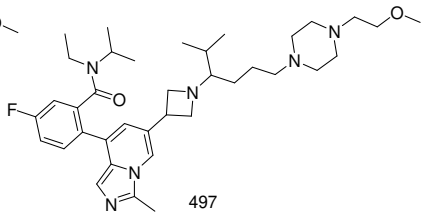

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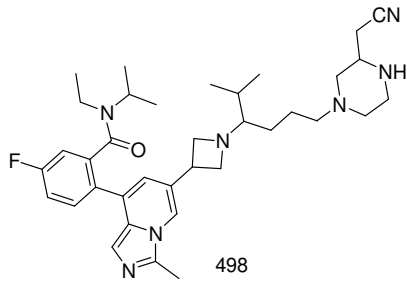
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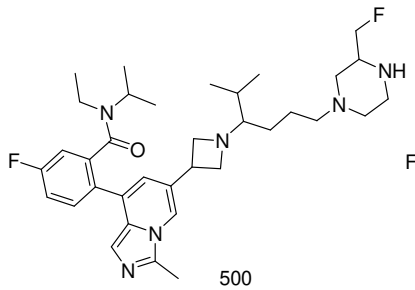
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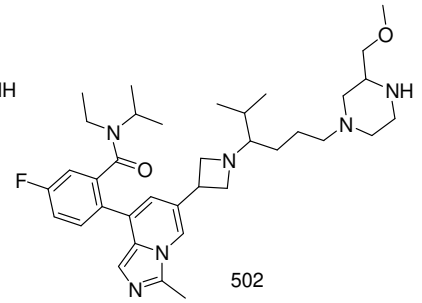
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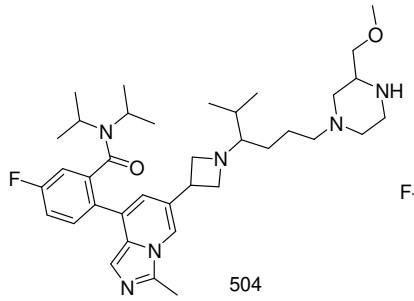
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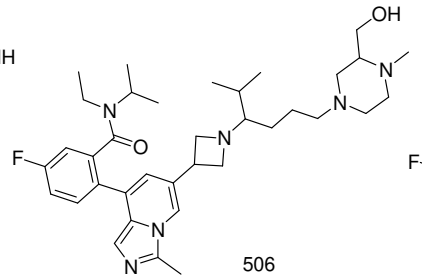
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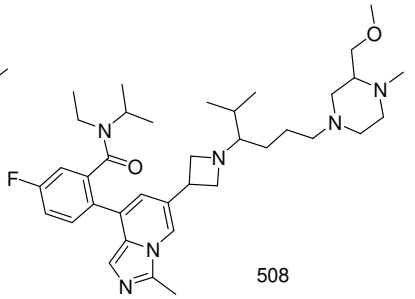
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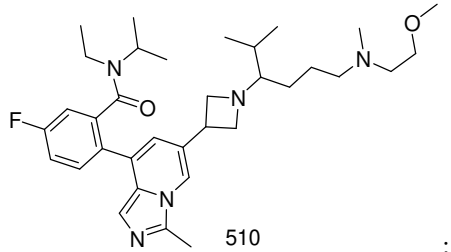
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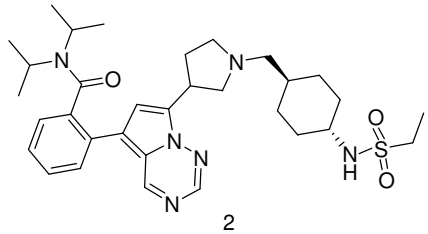
preferably, said stereoisomer is selected from the following structures: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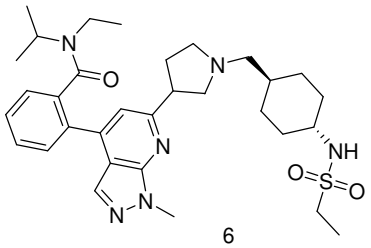
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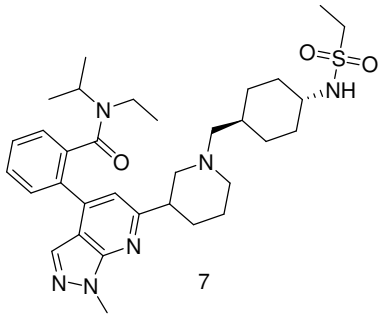
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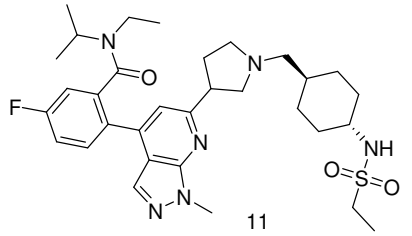
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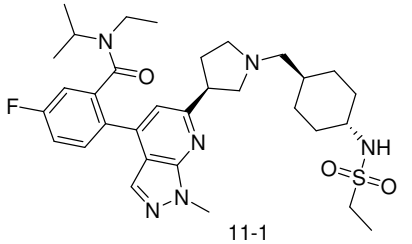
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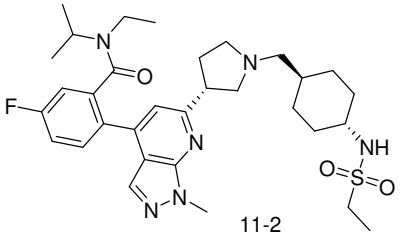
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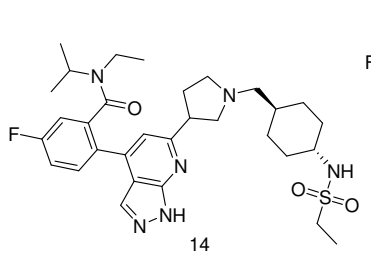

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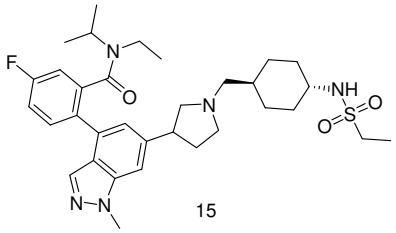

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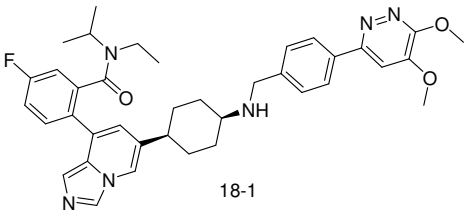

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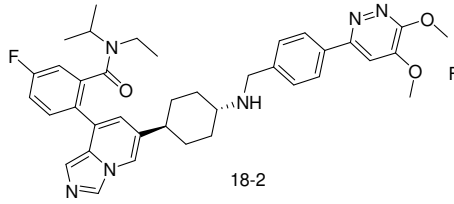

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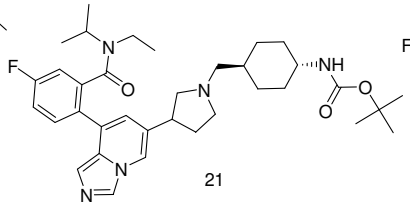

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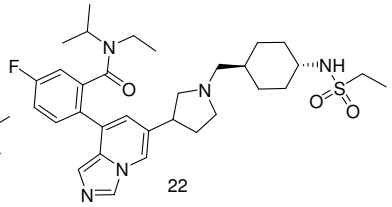

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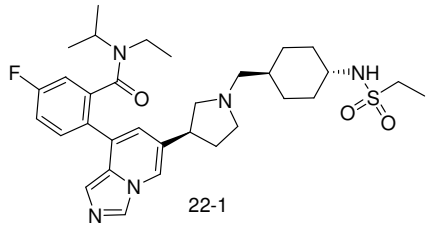

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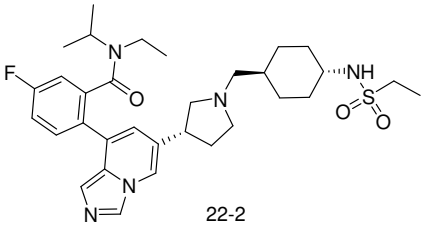

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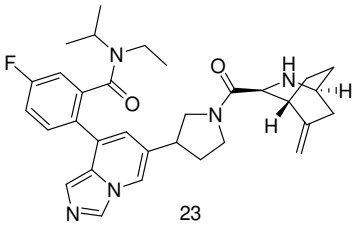

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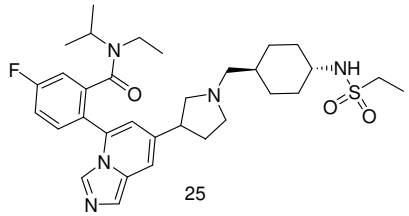

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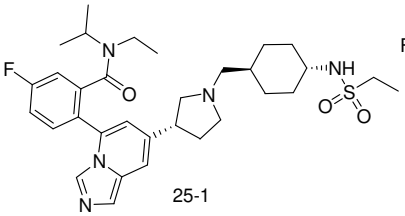

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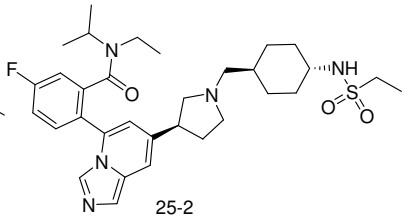

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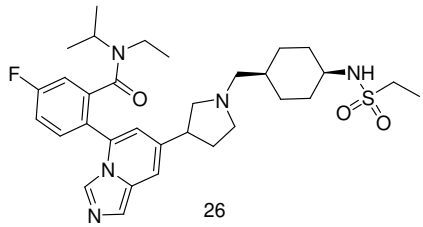

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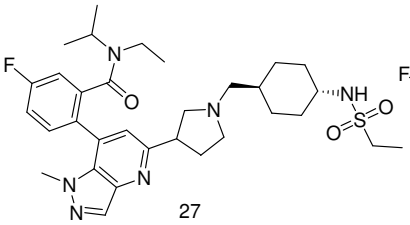

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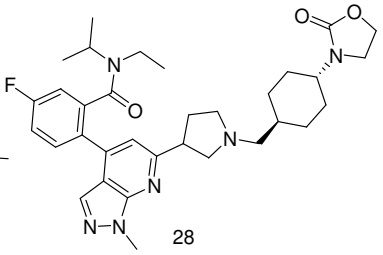

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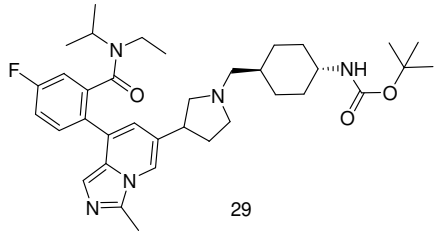

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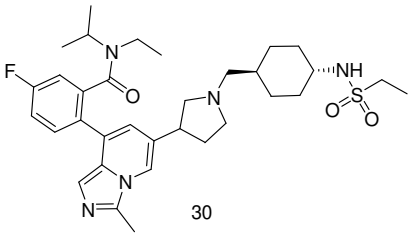

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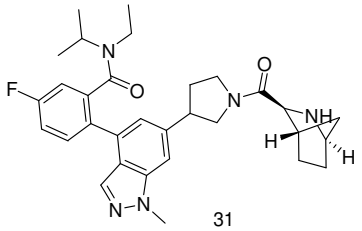

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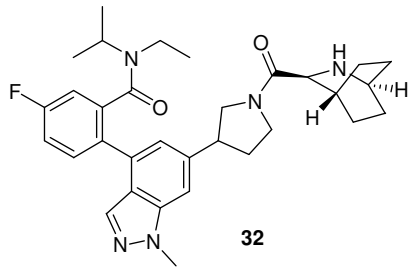

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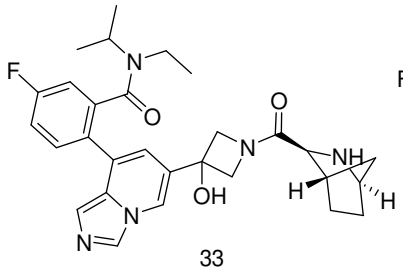

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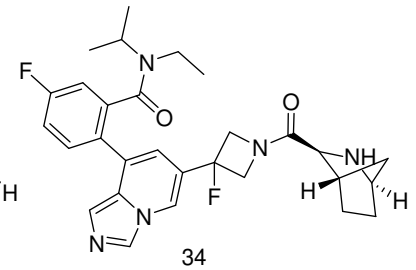

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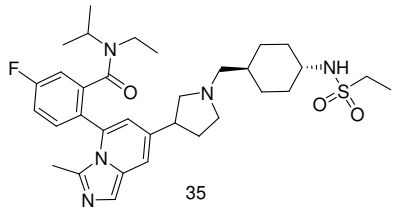

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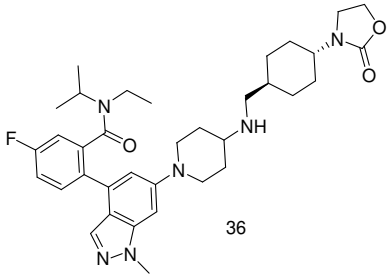

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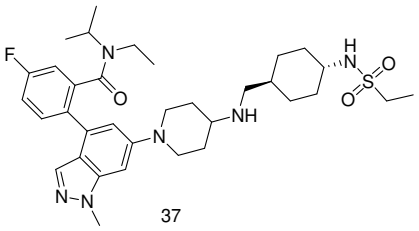

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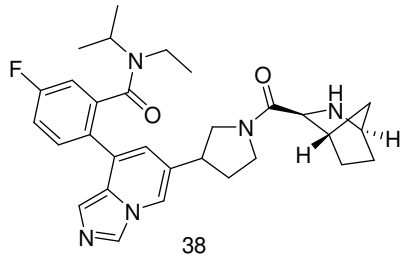

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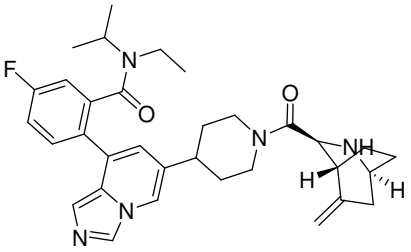

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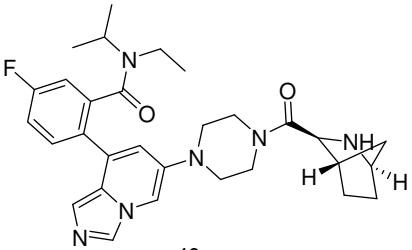

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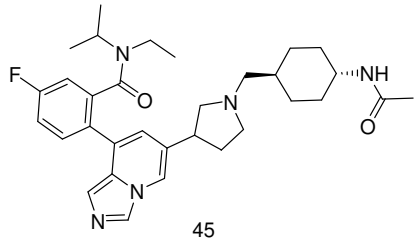

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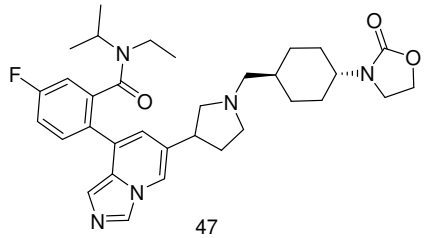

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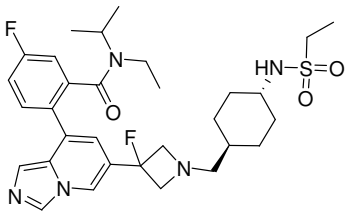

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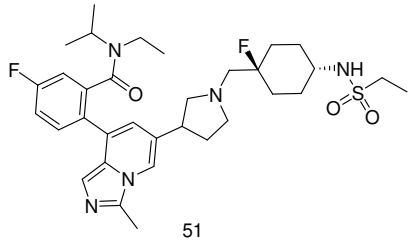

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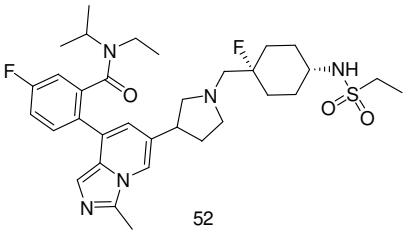

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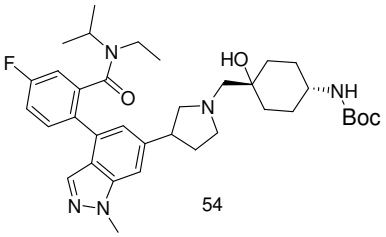

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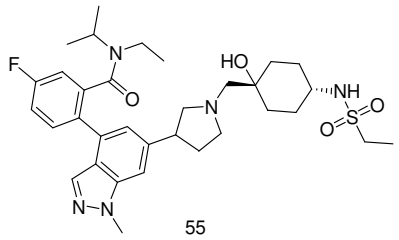

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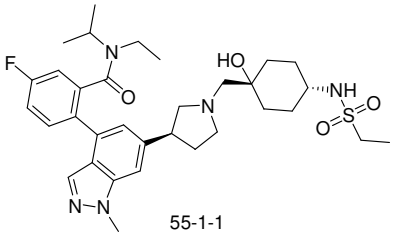

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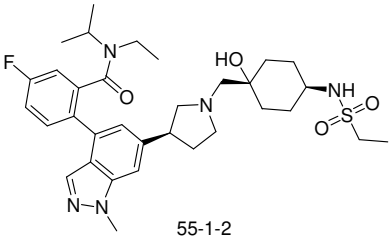

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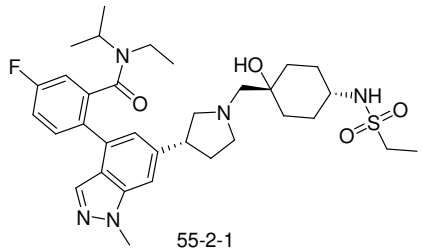

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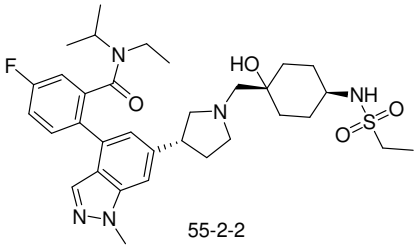

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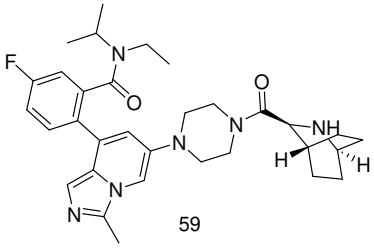

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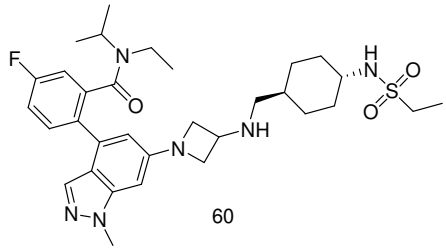

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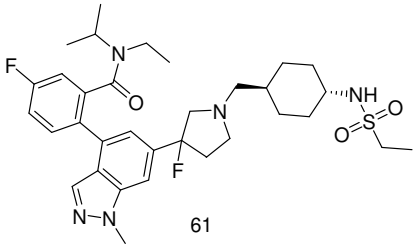

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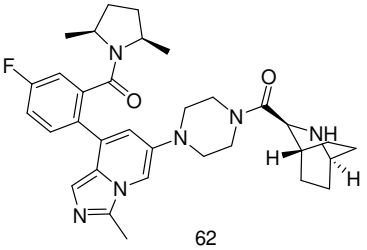

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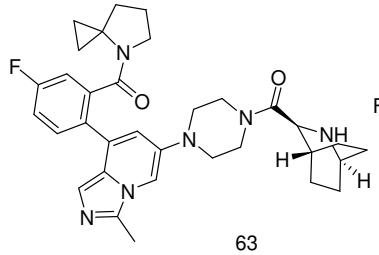

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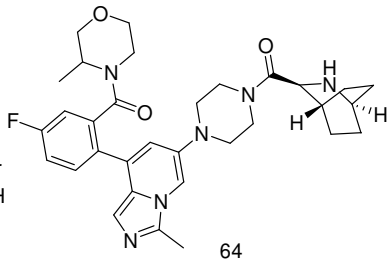

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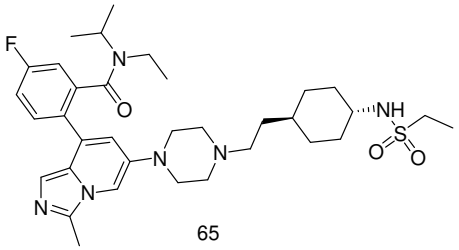

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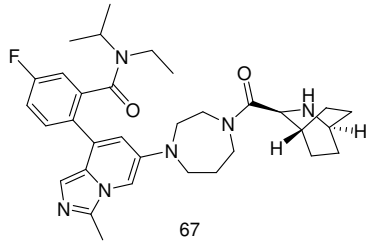

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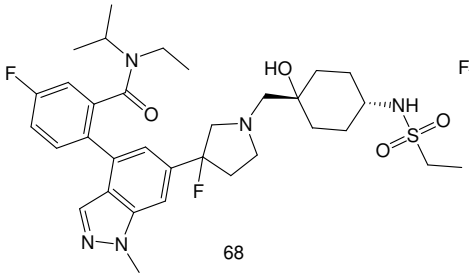

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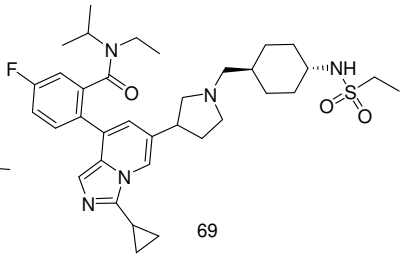

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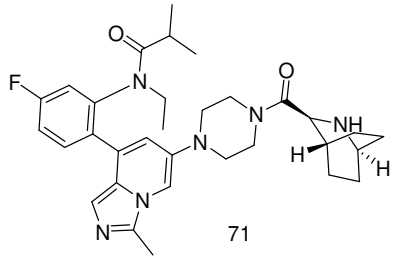

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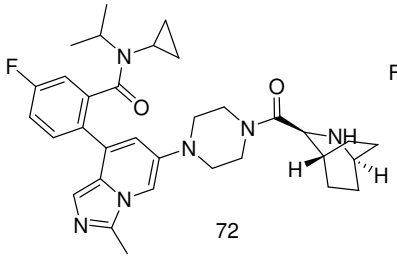

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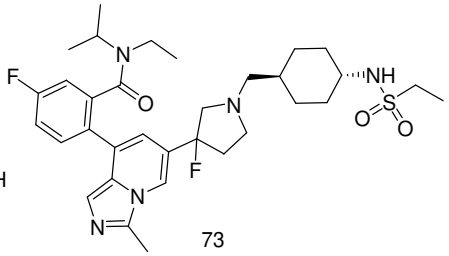

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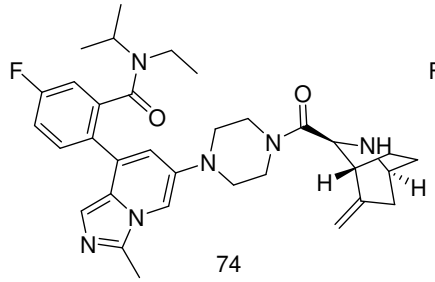

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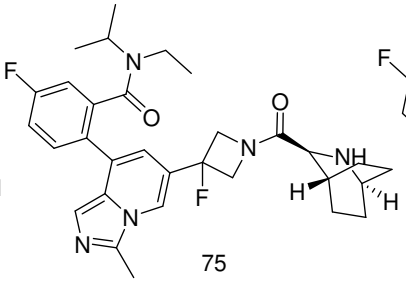

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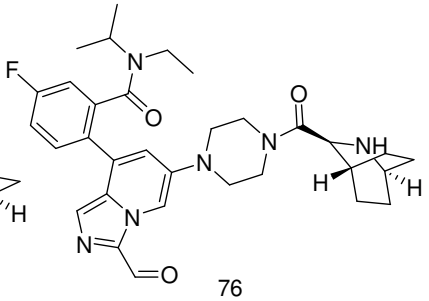

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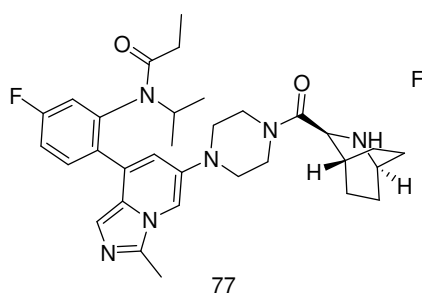

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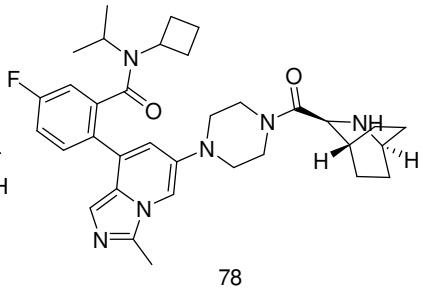

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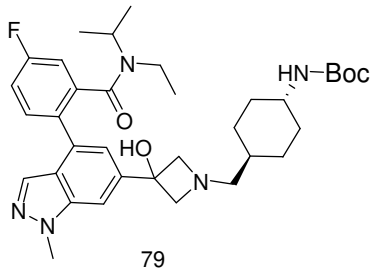

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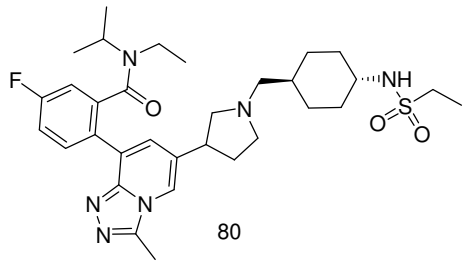

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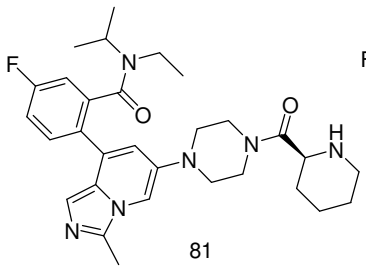

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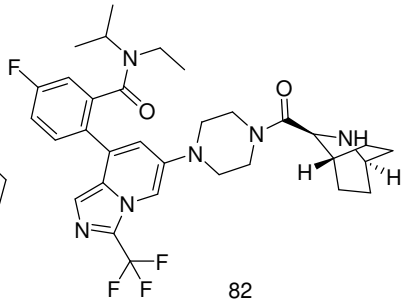

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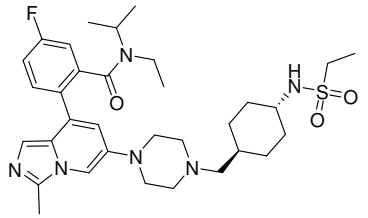

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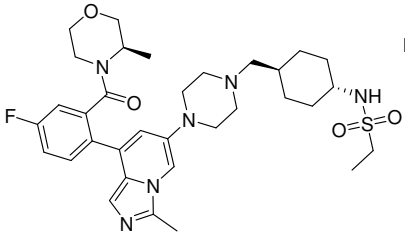

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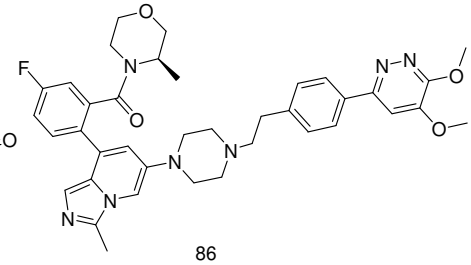

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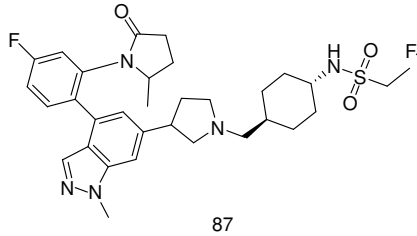

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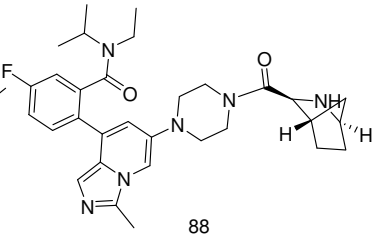

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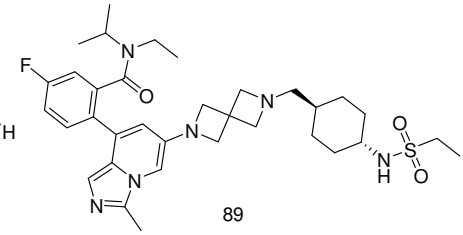

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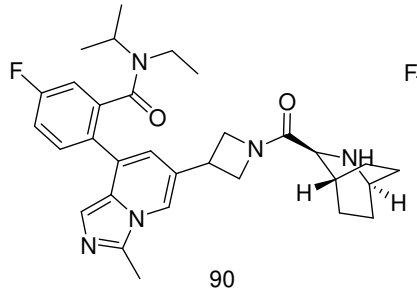

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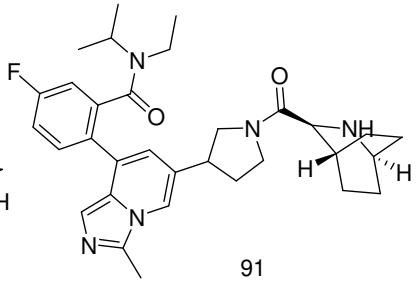

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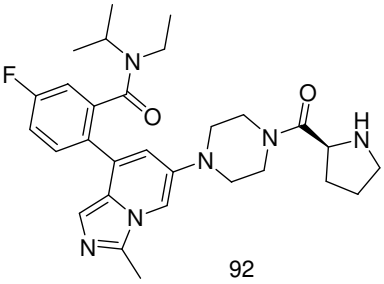

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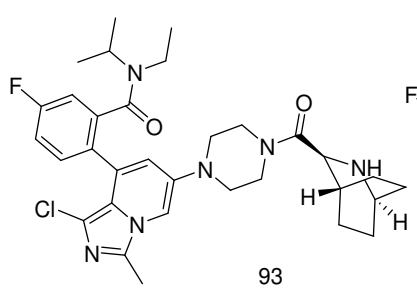

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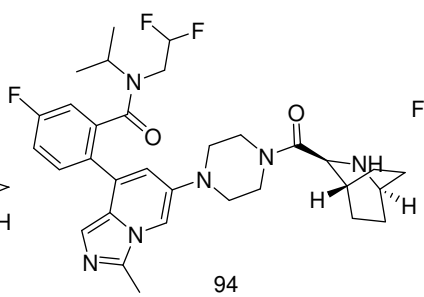

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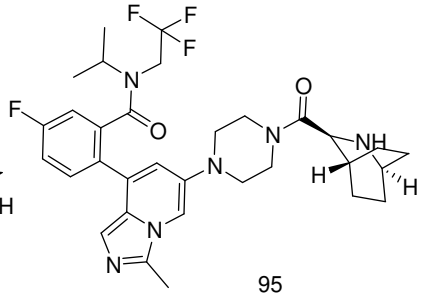

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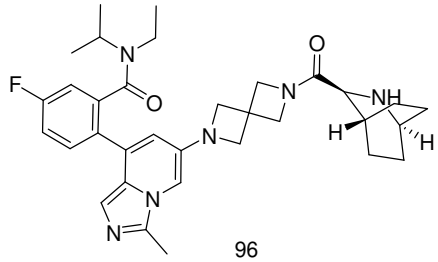

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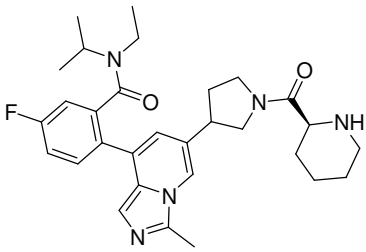

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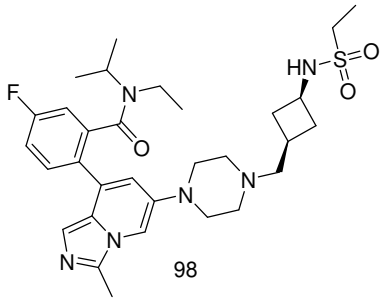

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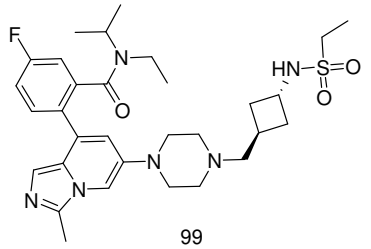

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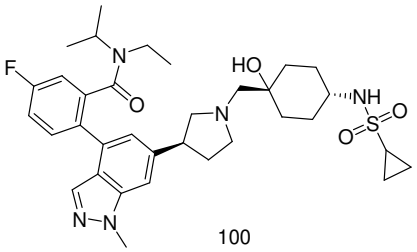

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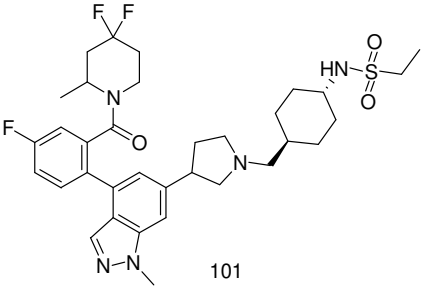

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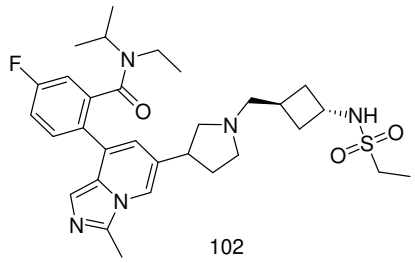

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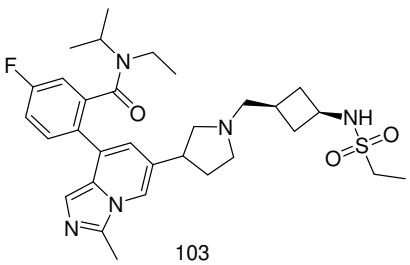

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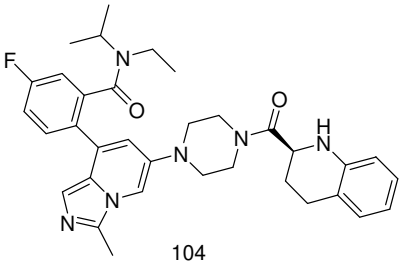

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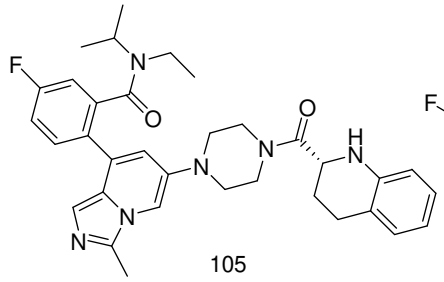

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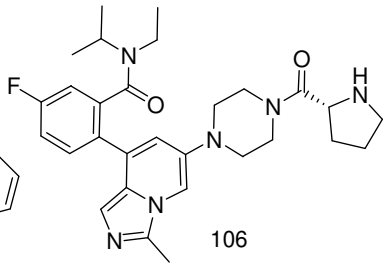

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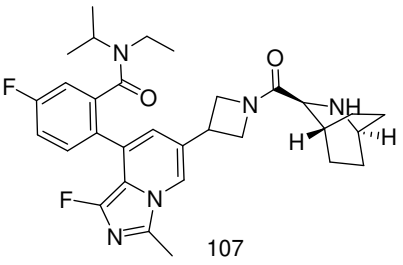

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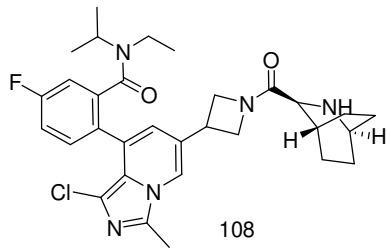

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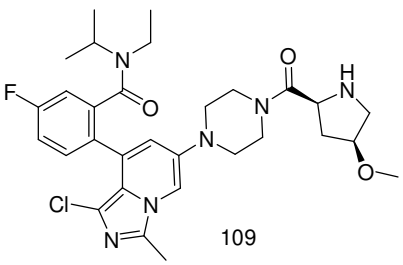

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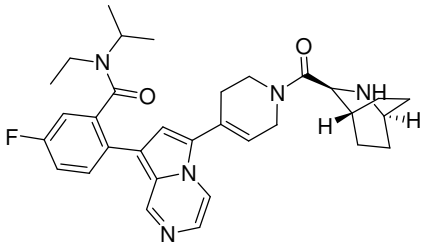

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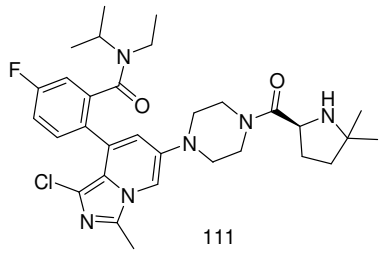

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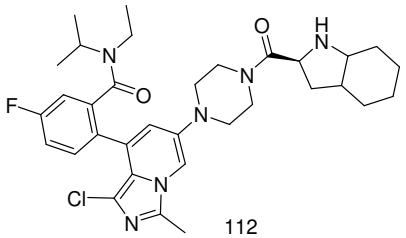

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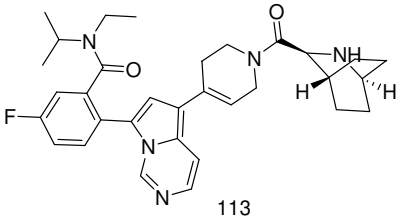

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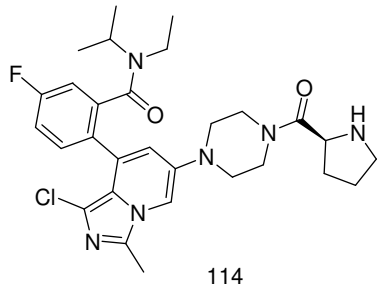

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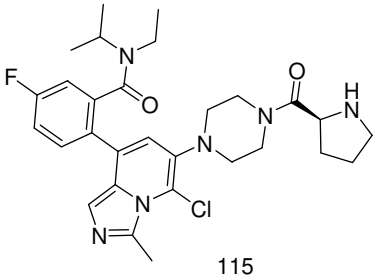

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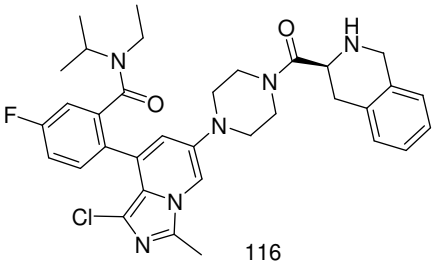

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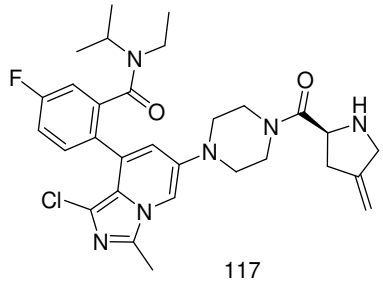

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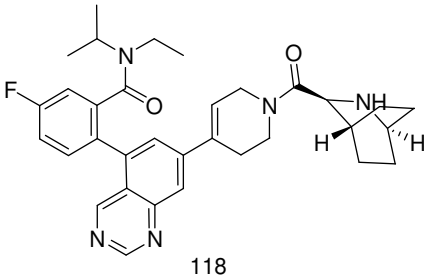

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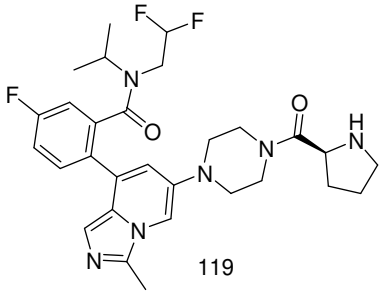

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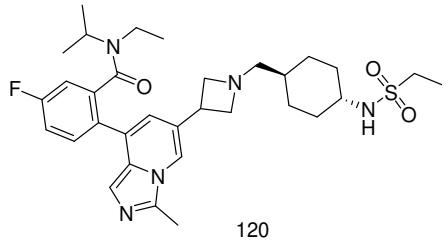

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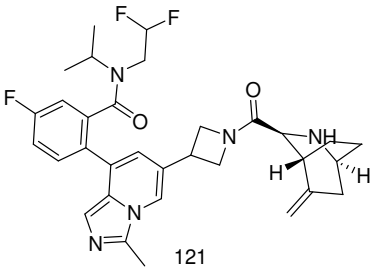

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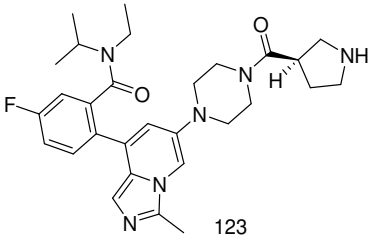

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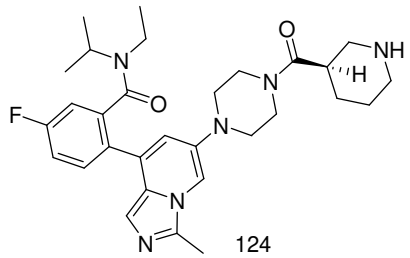

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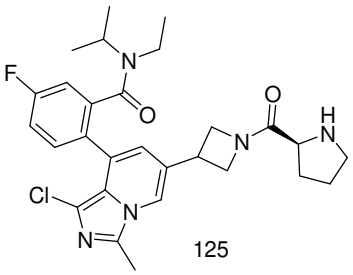

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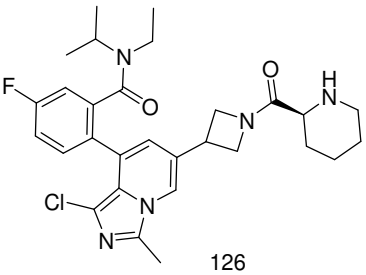

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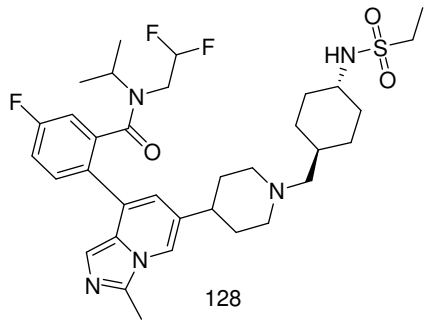

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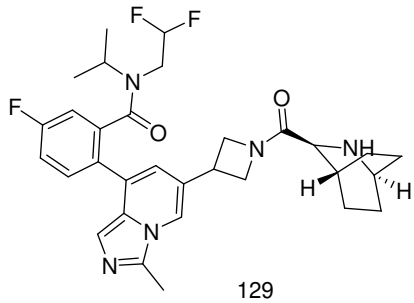

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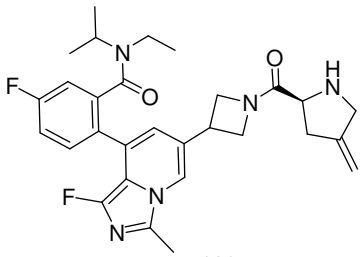

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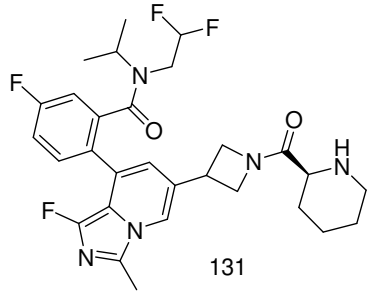

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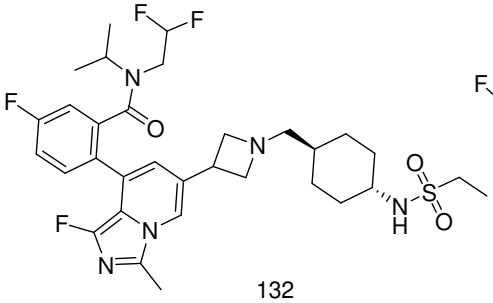

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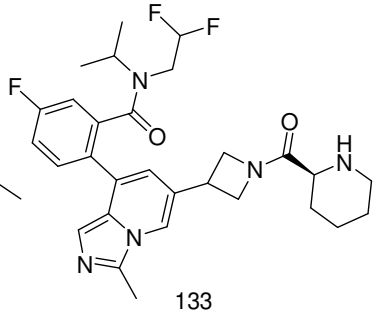

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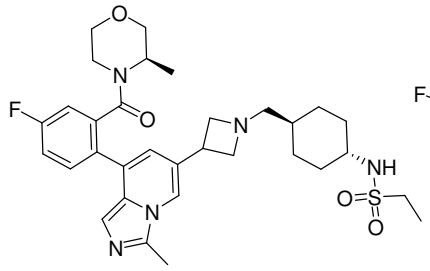

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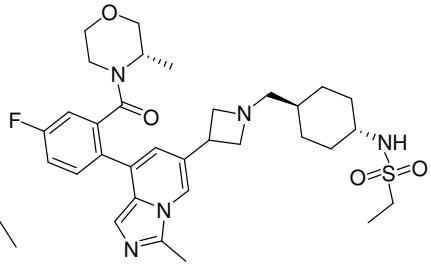

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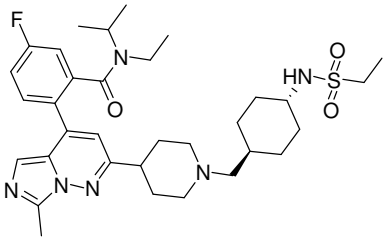

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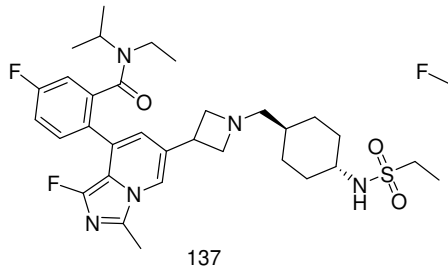

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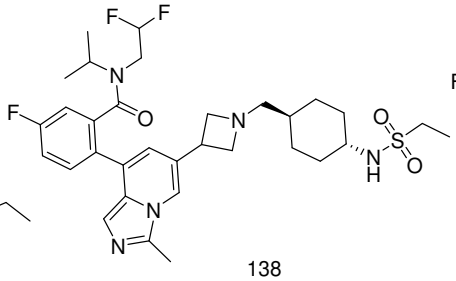

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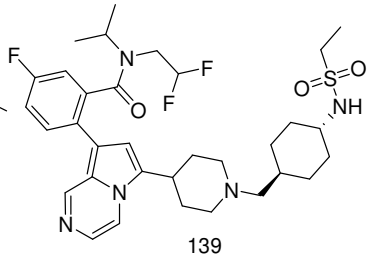

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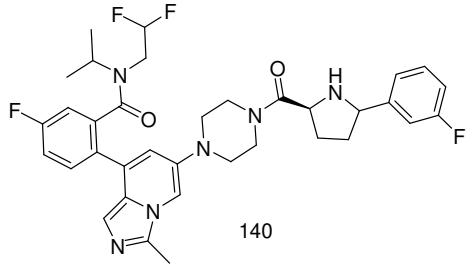

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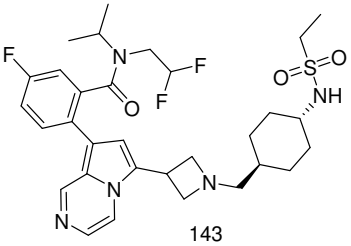

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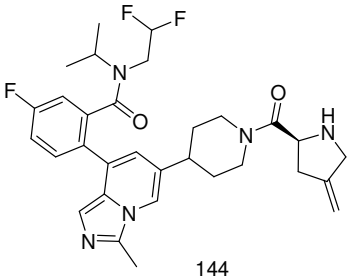

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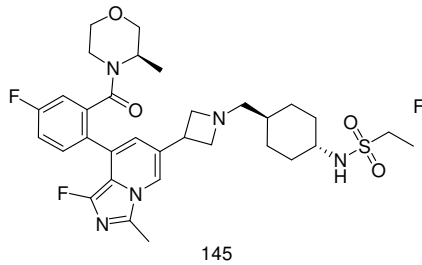

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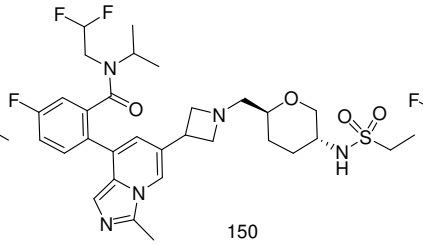

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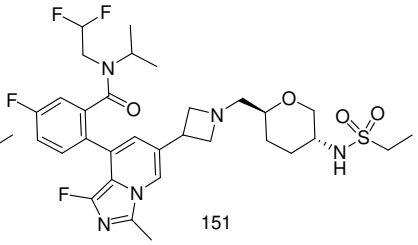

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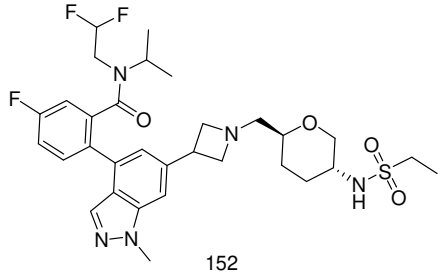

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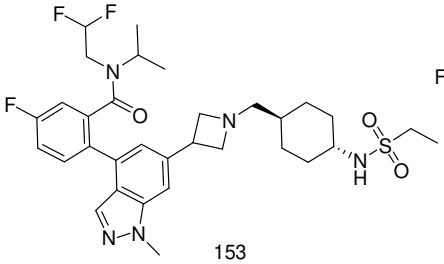

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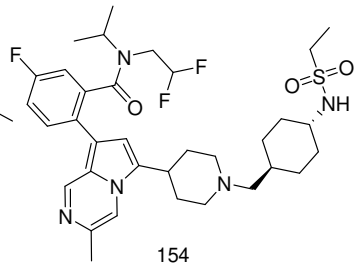

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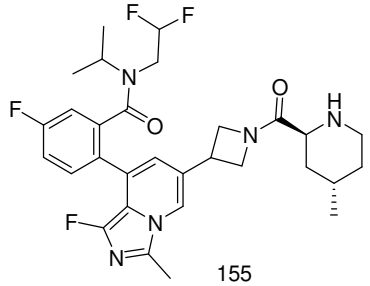

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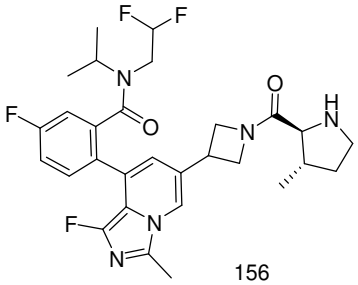

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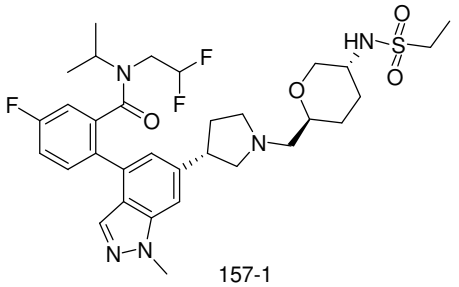

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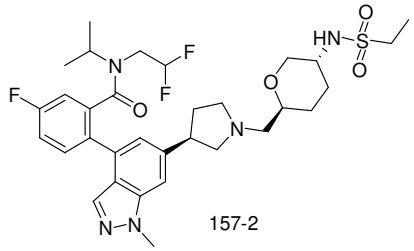

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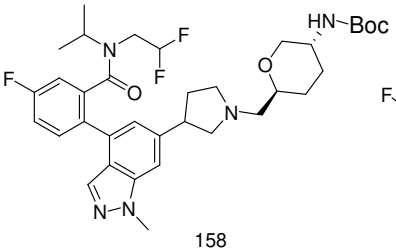

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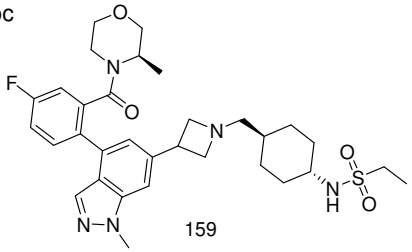

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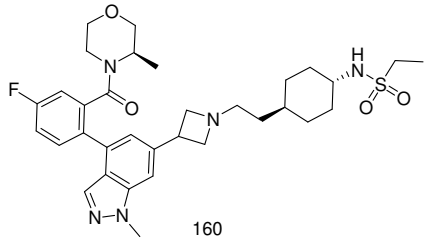

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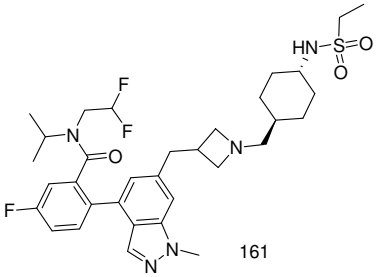

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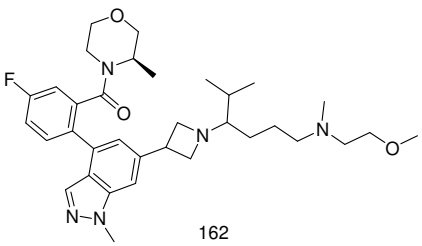

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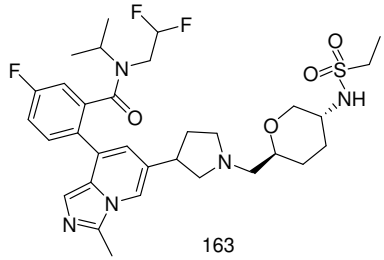

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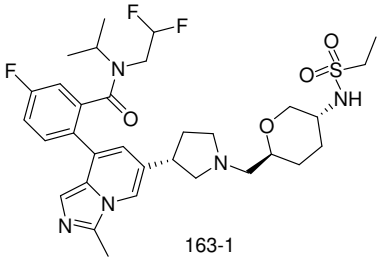

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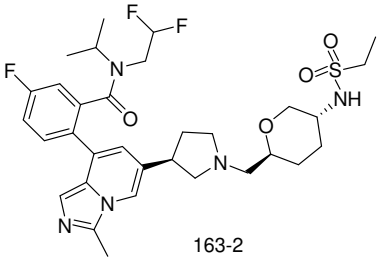

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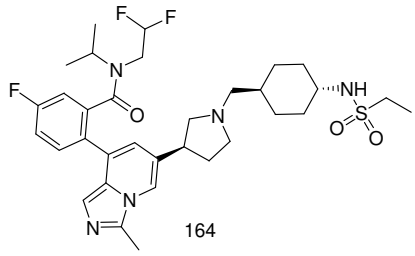

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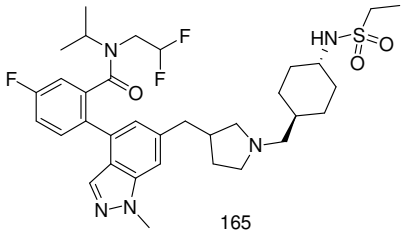

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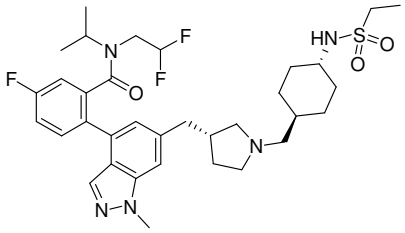

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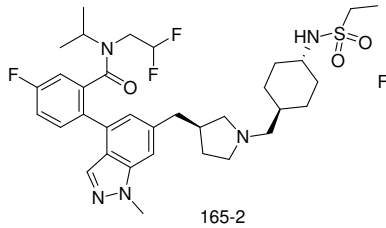

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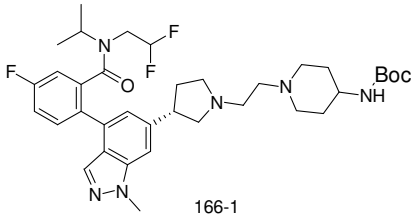

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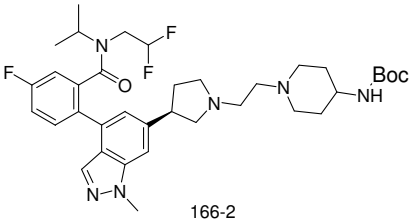

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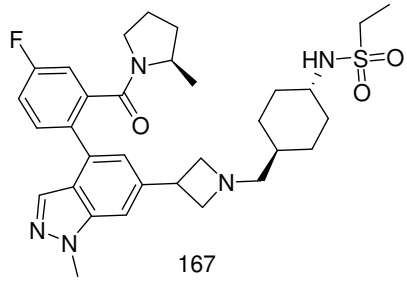

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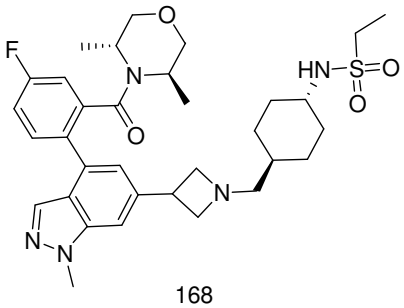

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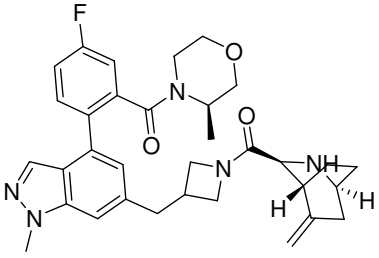

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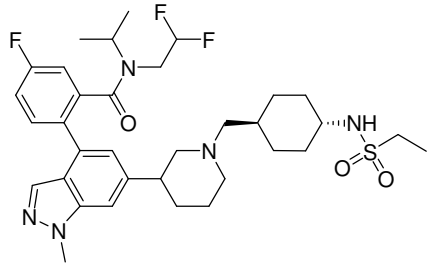

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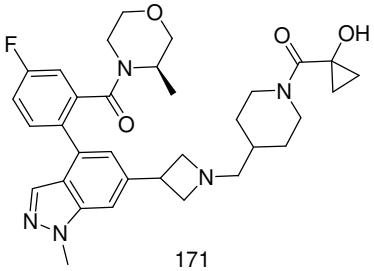

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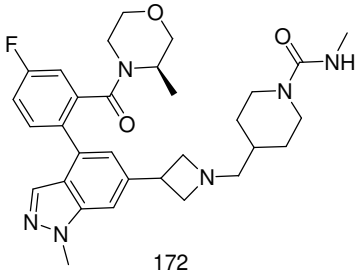

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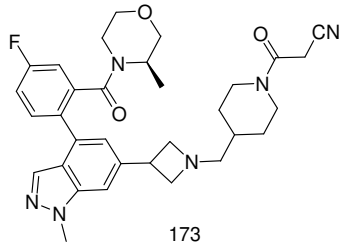

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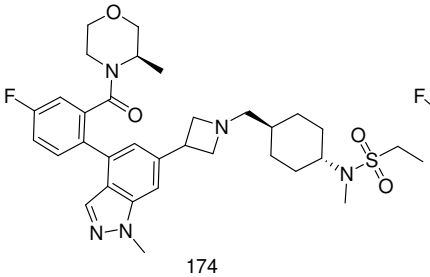

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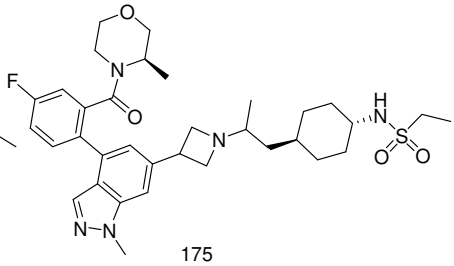

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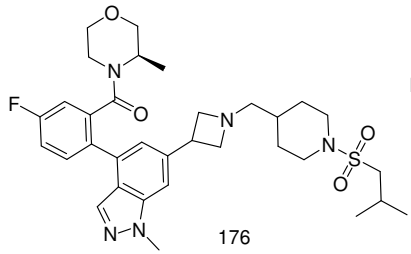

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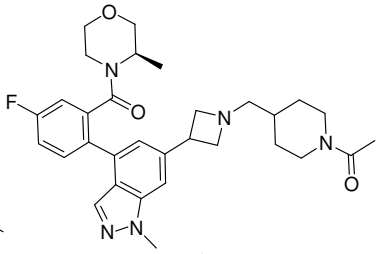

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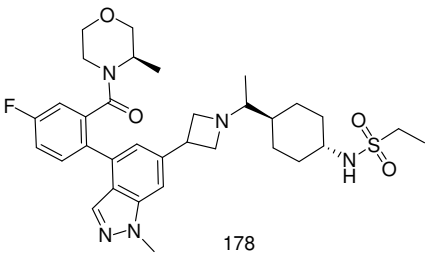

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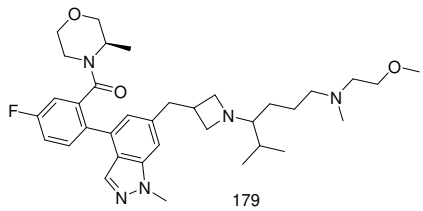

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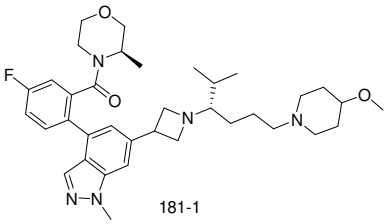
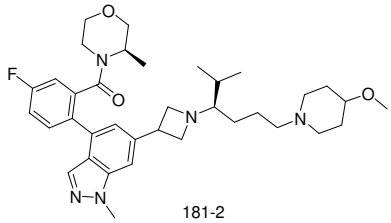


181-1



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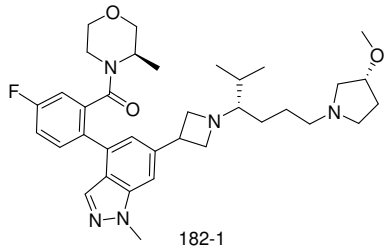
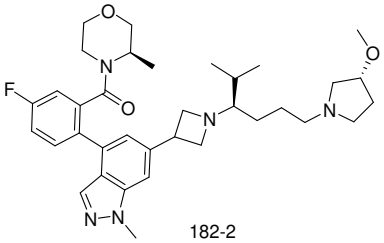


182-1



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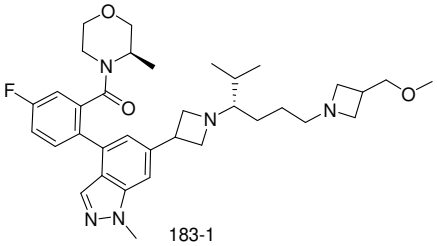

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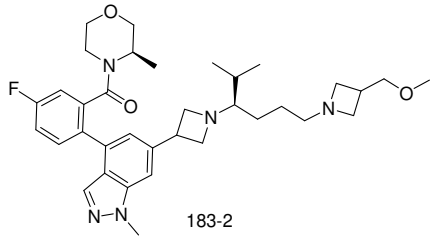

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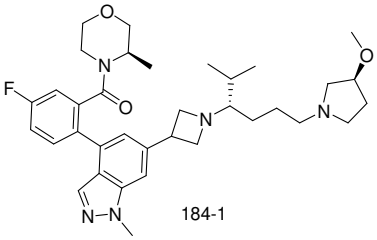

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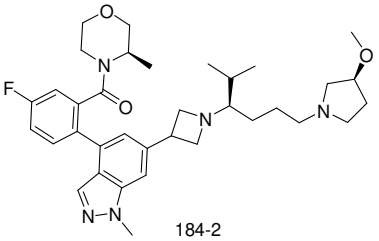

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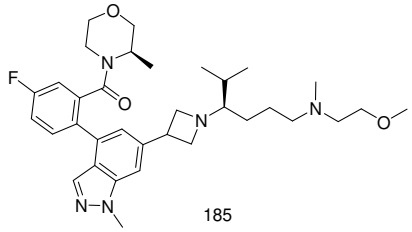

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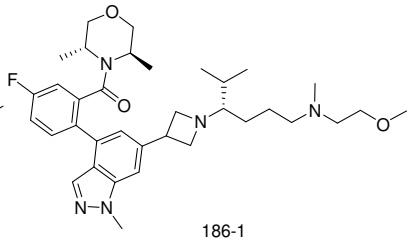

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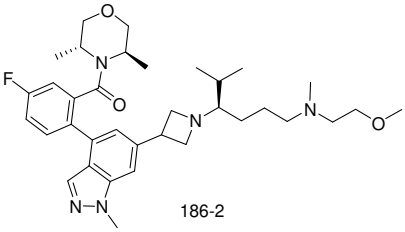
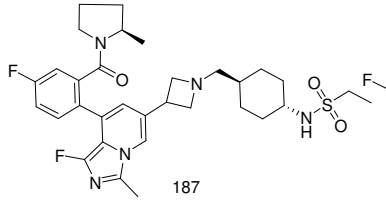


186-2



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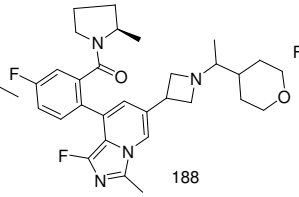

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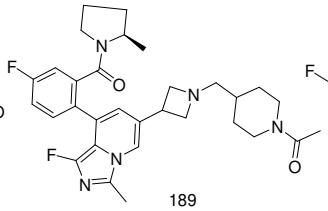

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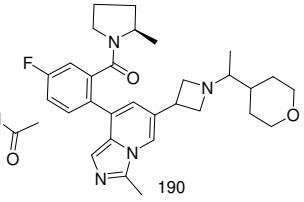

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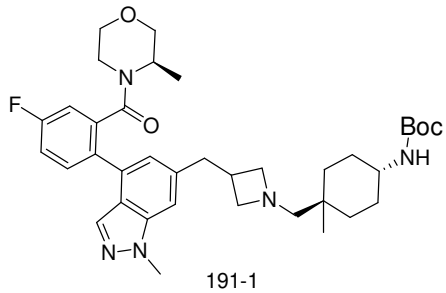
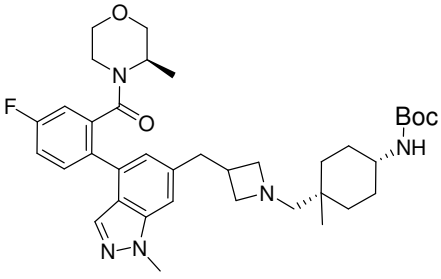
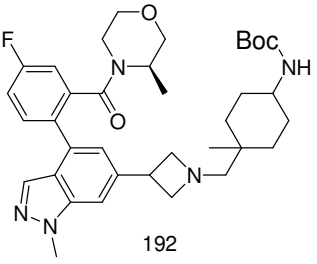


191-1



191-2



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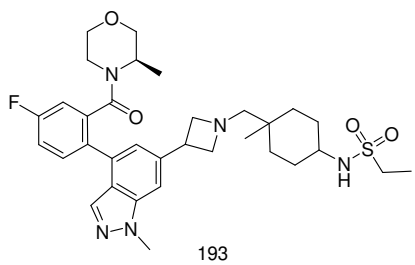

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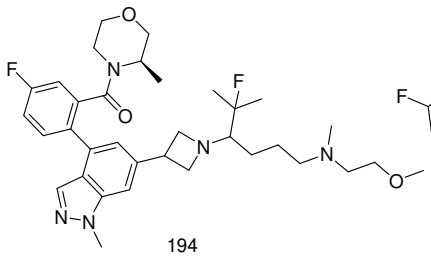

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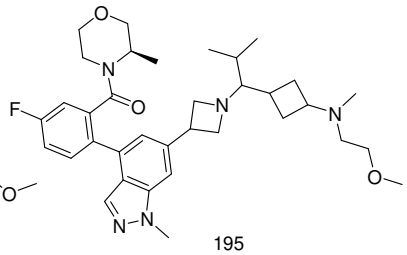

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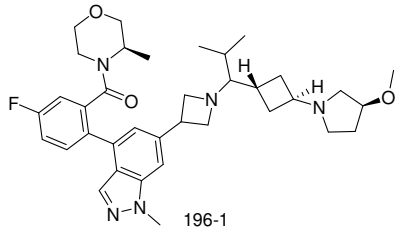
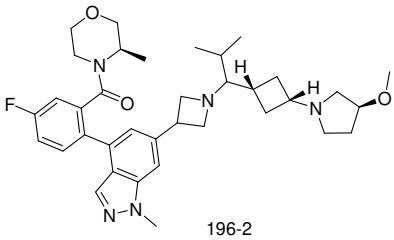
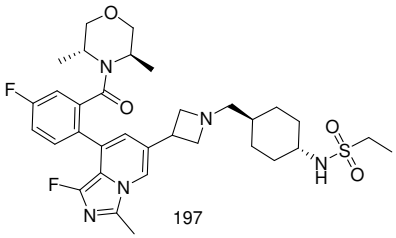


196-1



196-2



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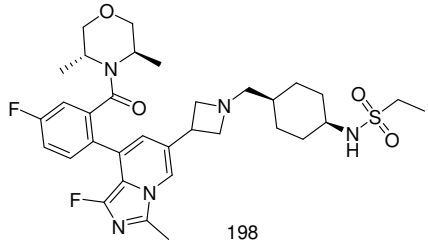

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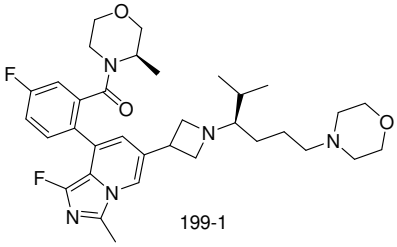

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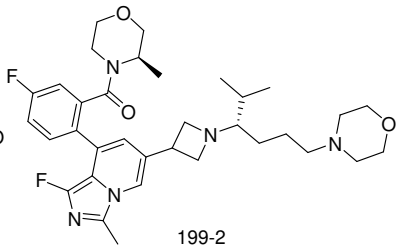

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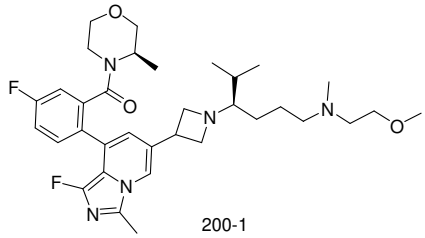

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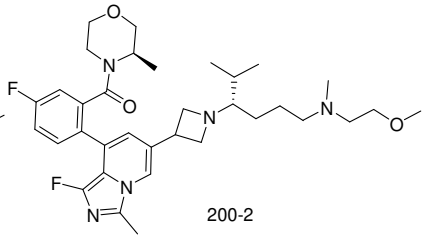

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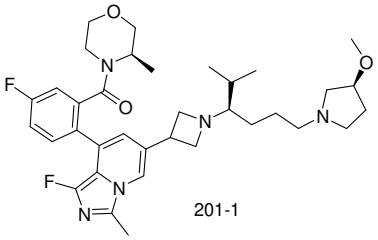

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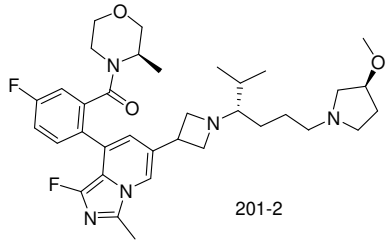

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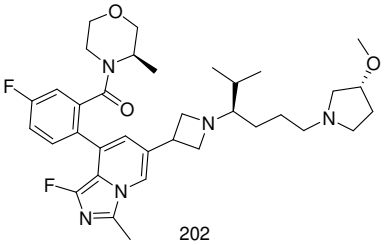

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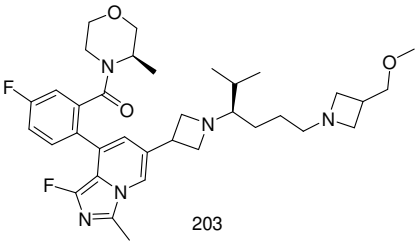

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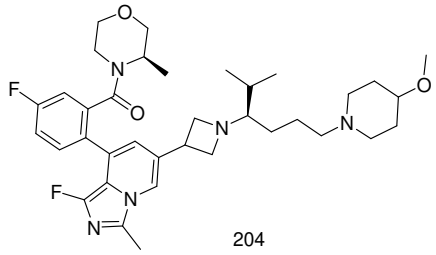

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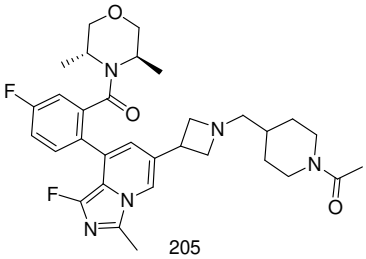

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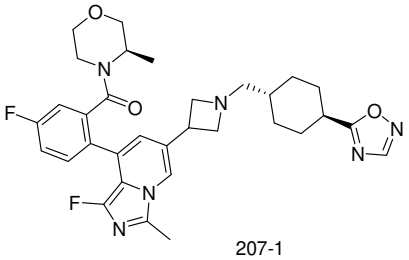

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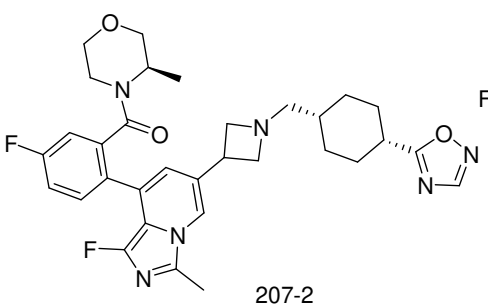

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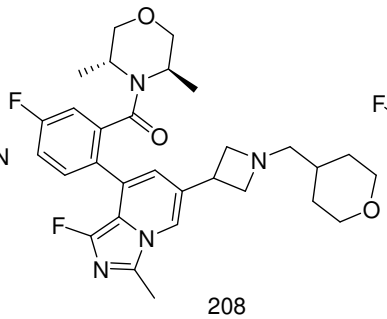

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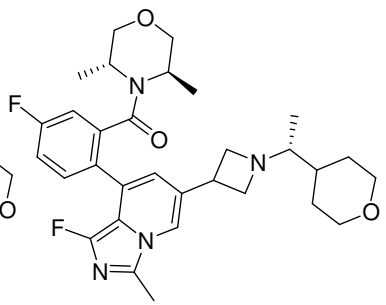

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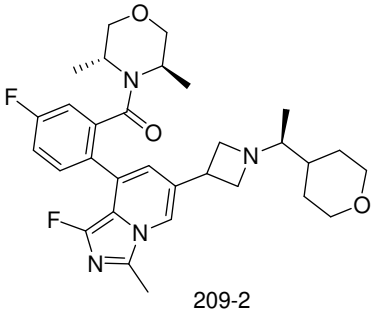

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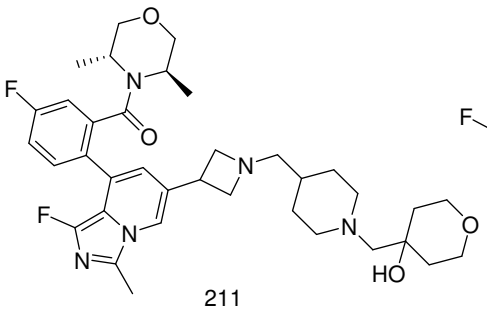

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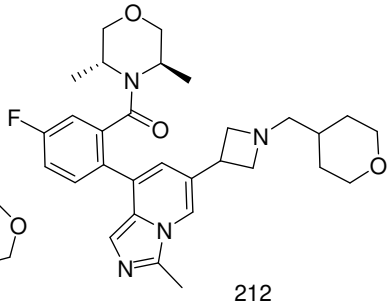

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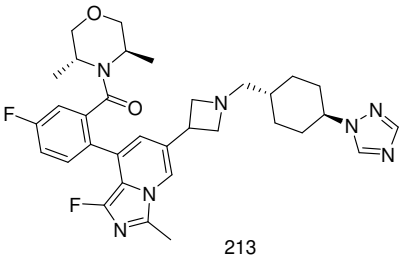

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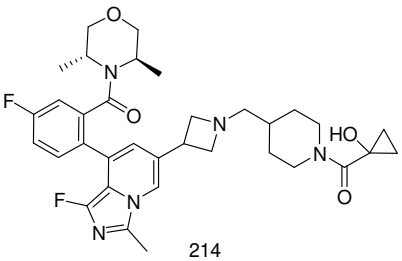

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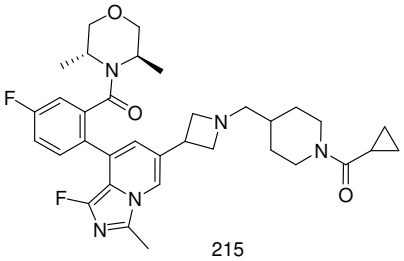

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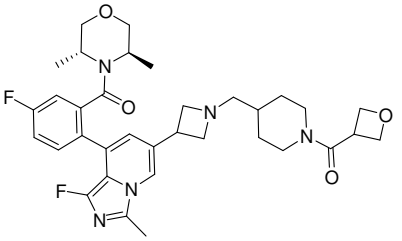

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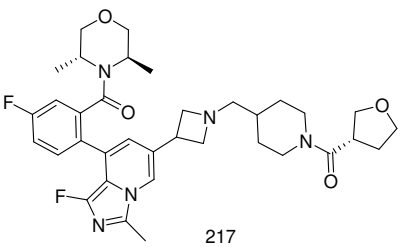

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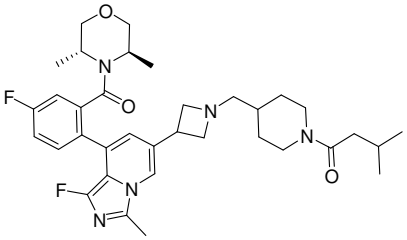

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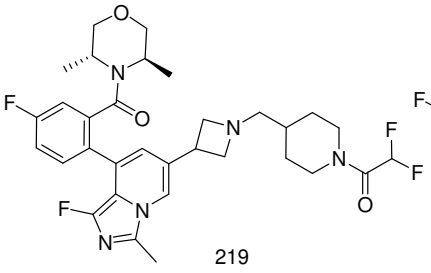

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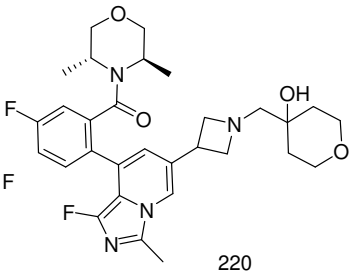

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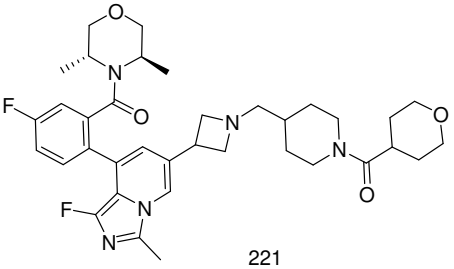

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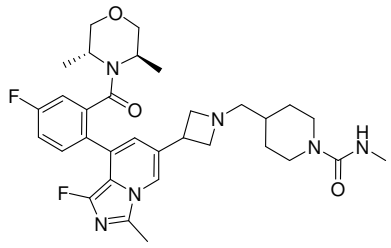

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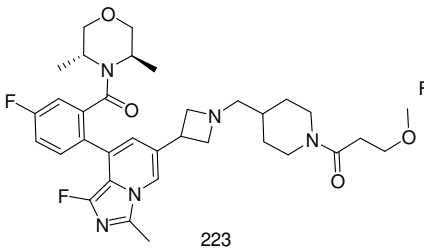

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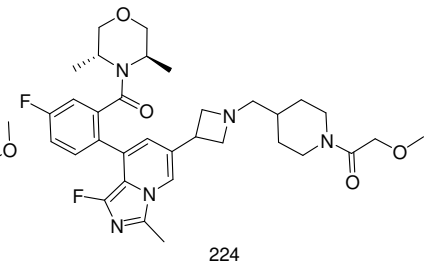

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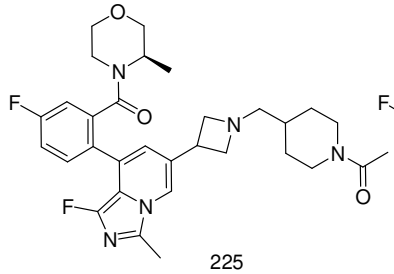

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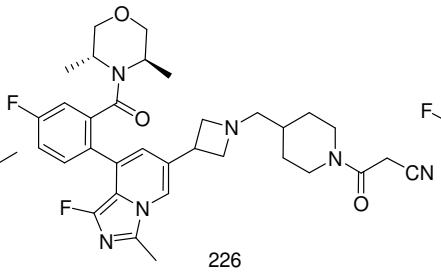

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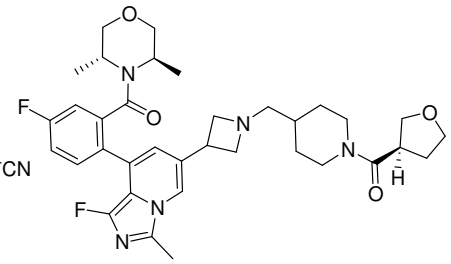

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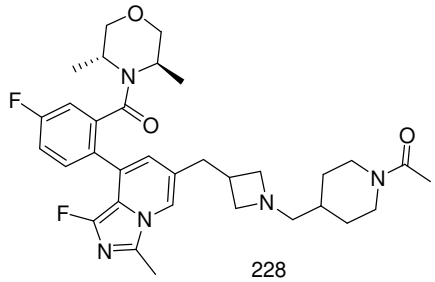

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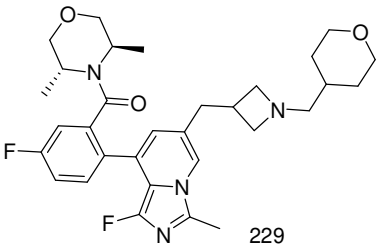

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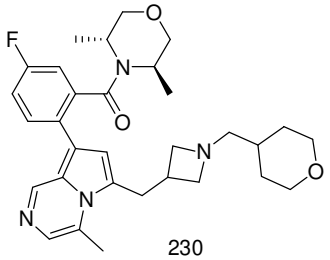

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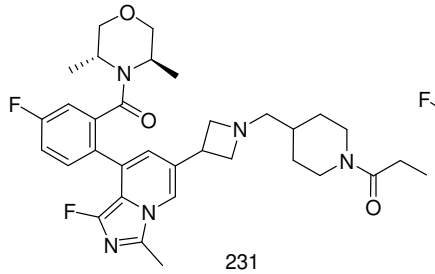

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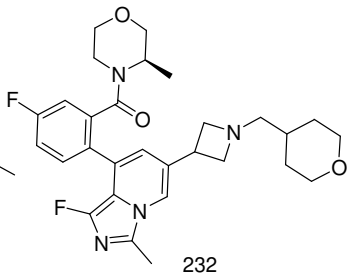

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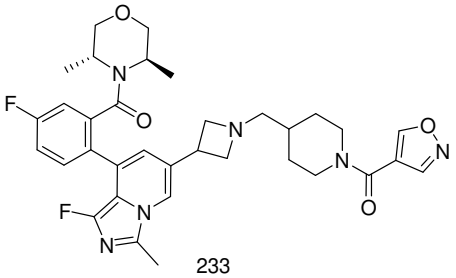

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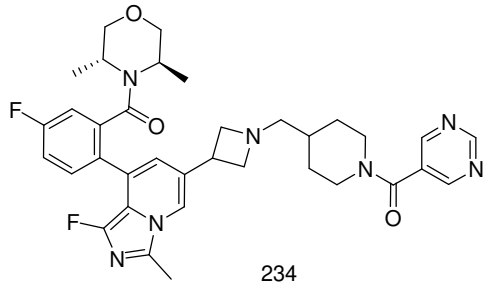

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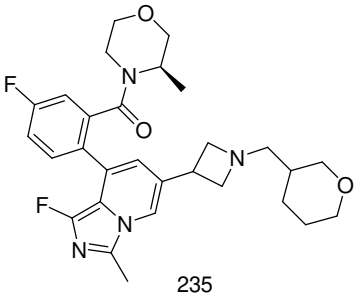

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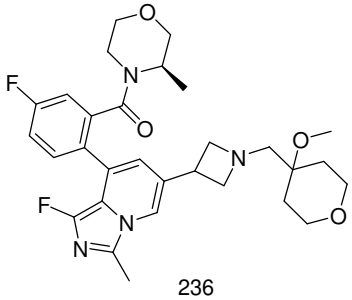

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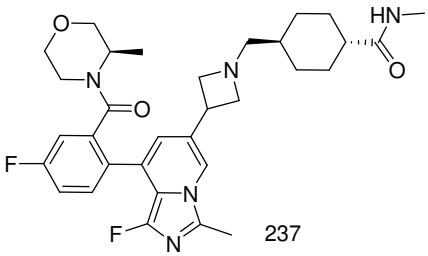

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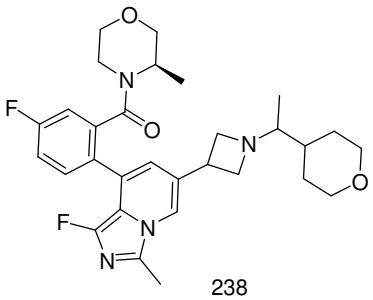

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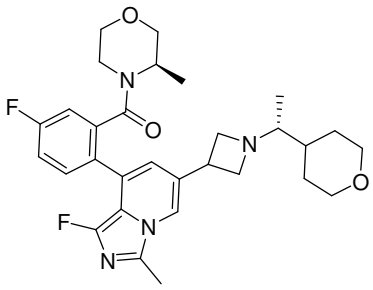

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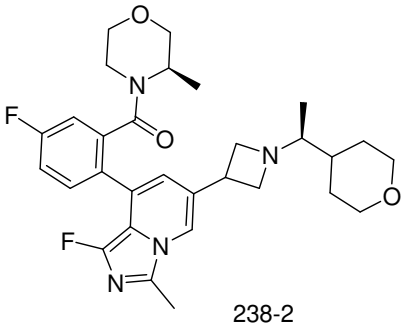

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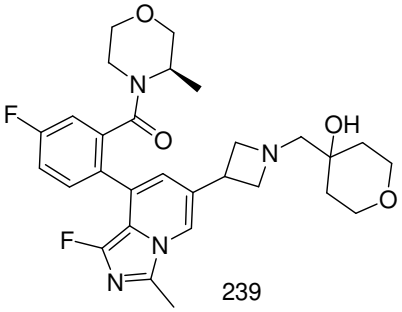

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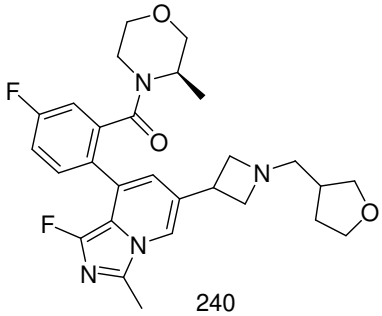

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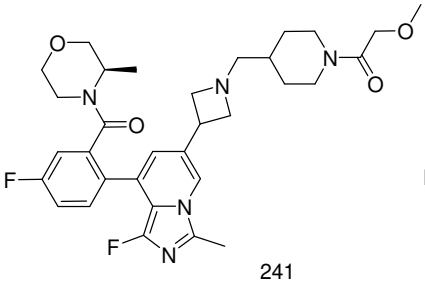

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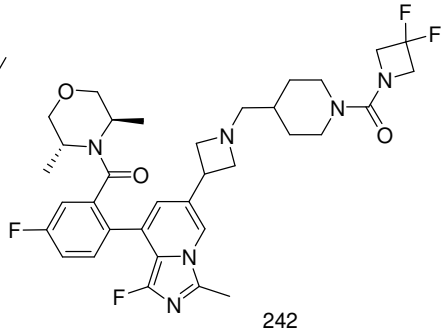

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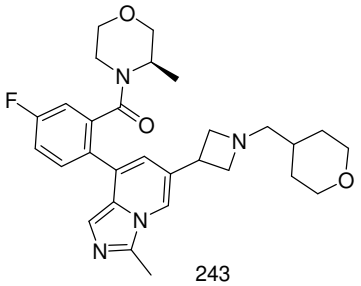

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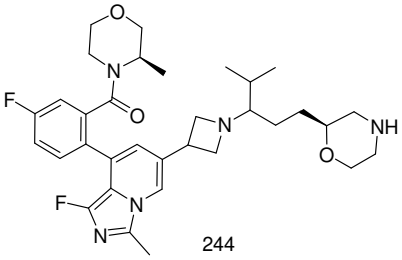

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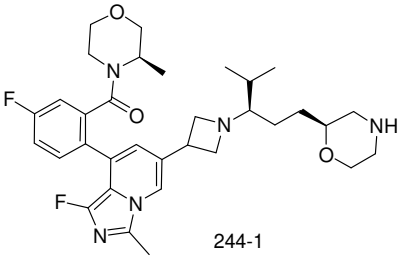

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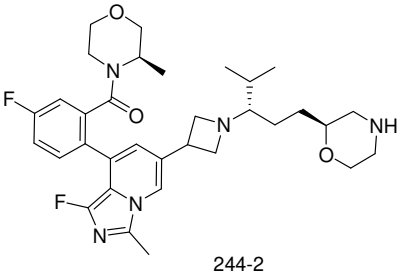

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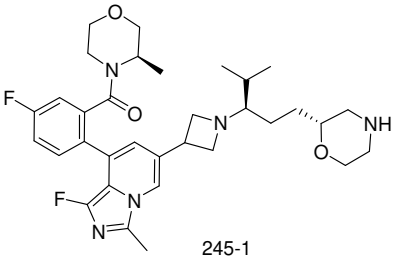

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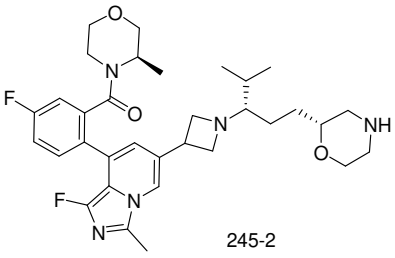

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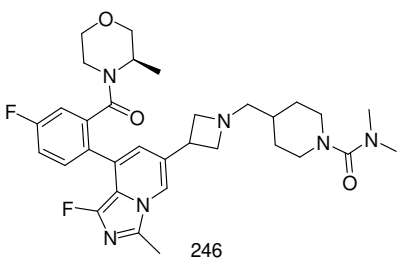

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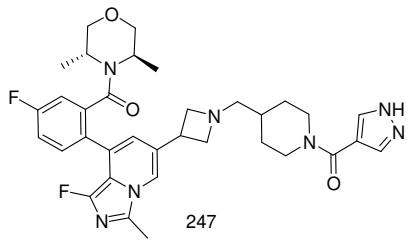

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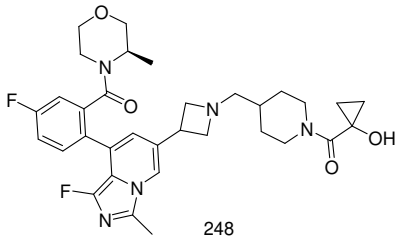

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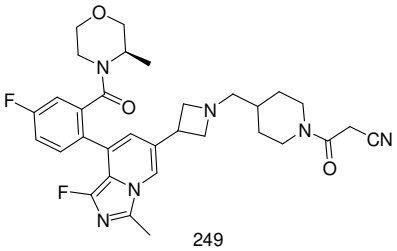

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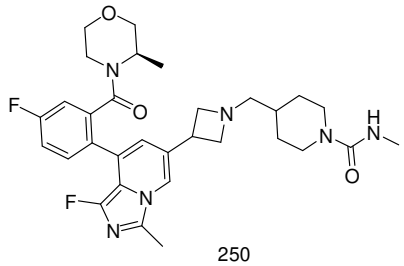

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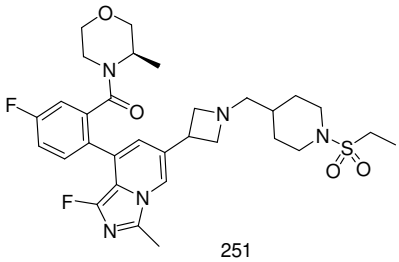

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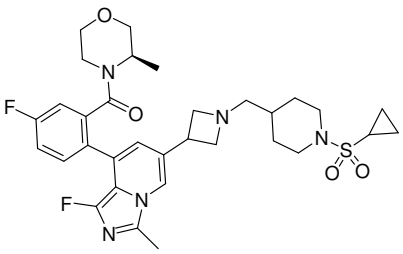

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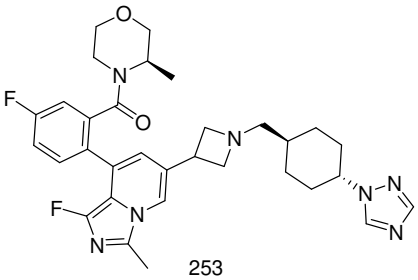

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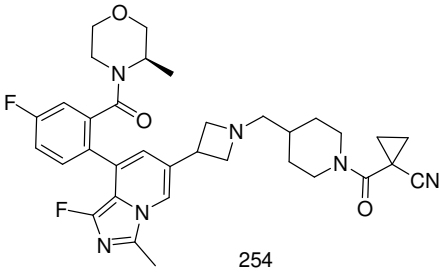

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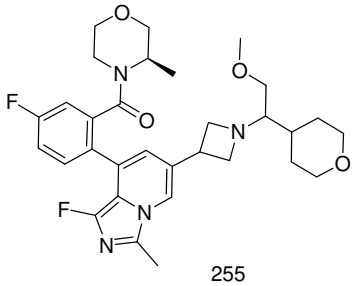

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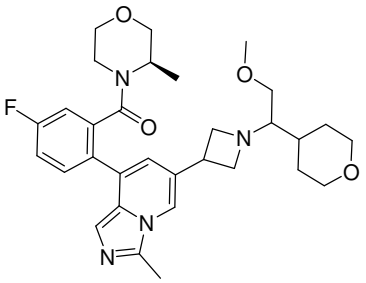

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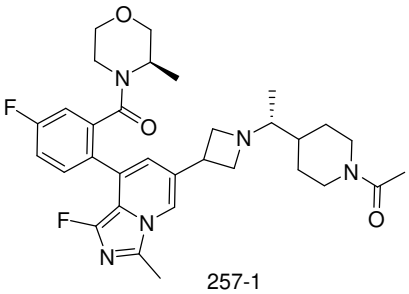

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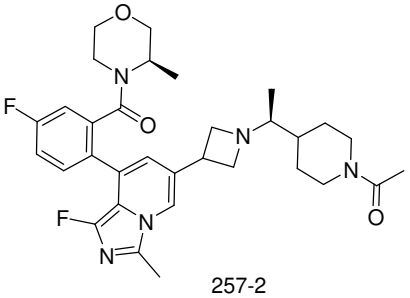

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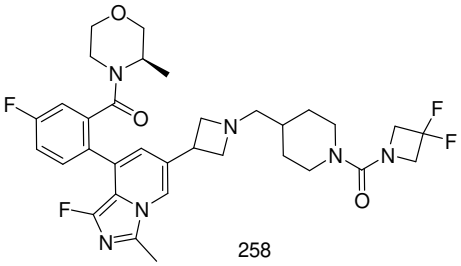

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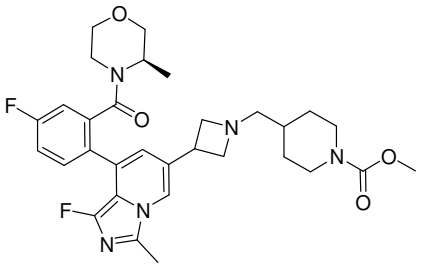

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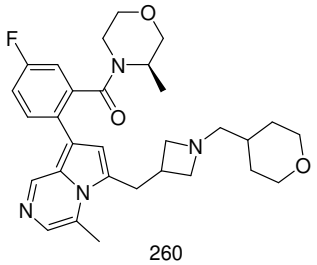

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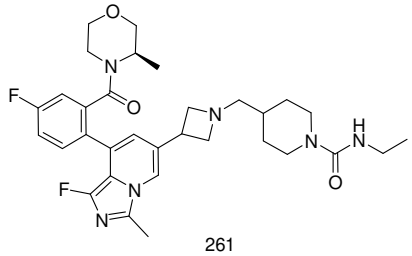

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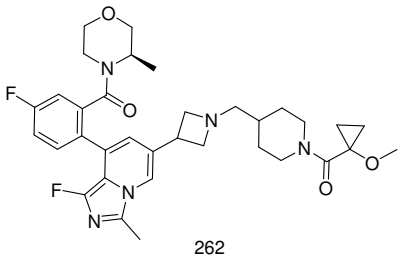

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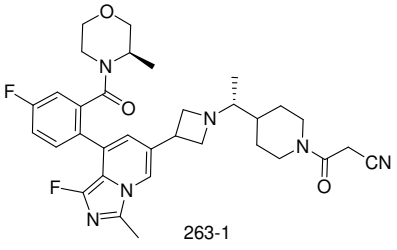

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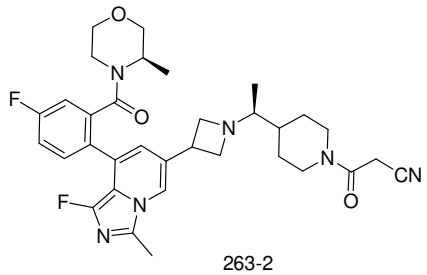

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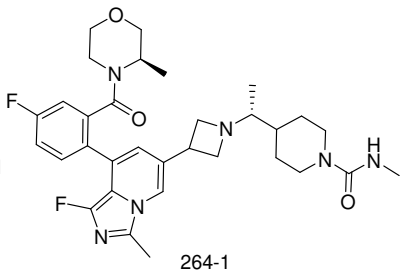

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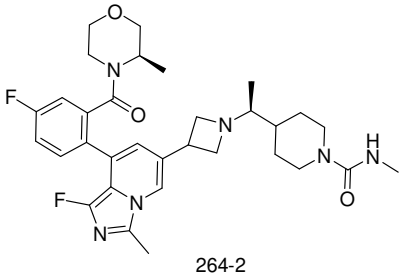

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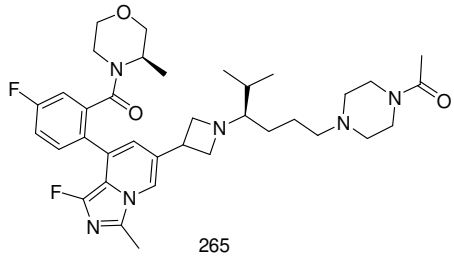

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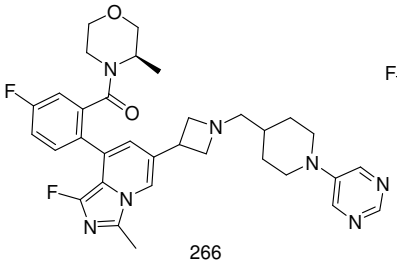

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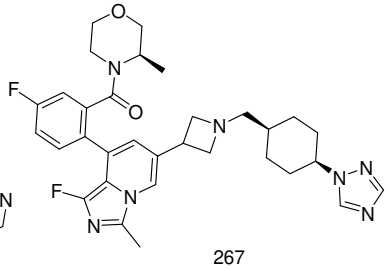

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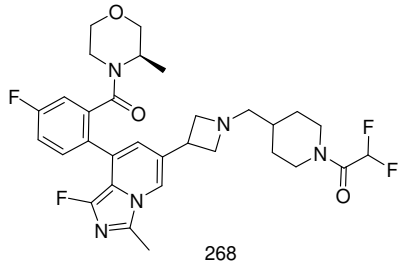

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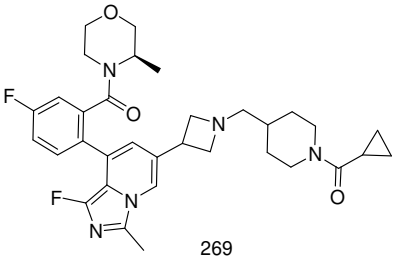

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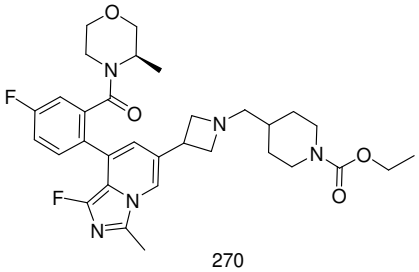

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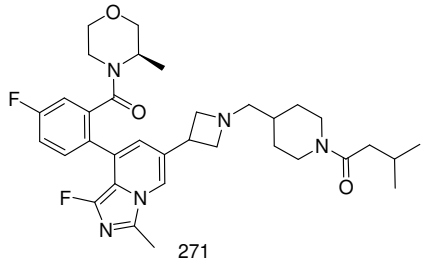

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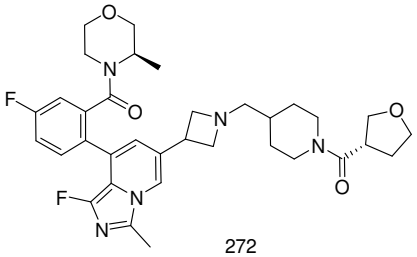

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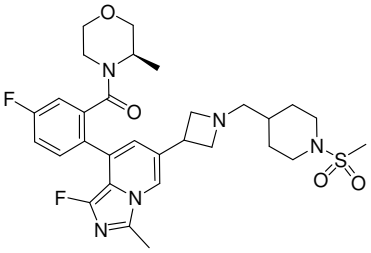

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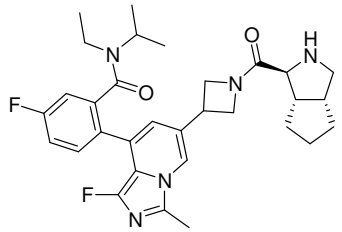

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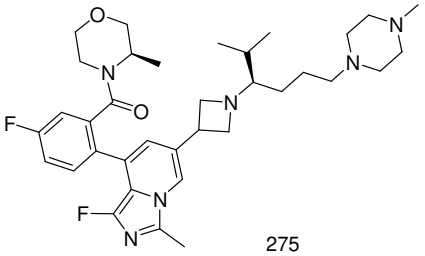

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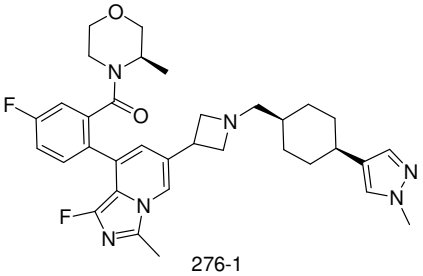

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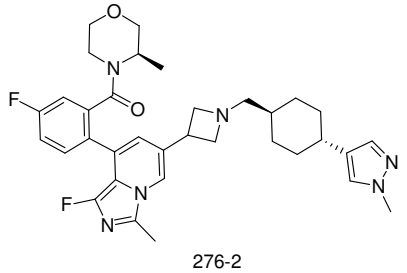

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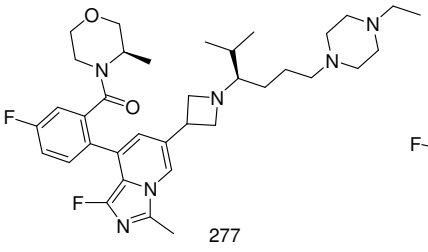

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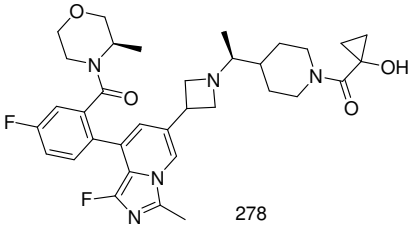

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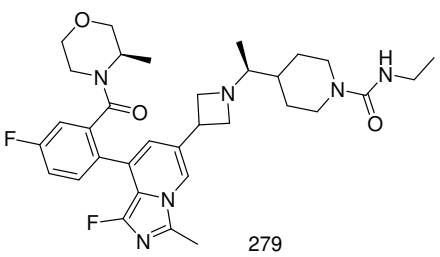

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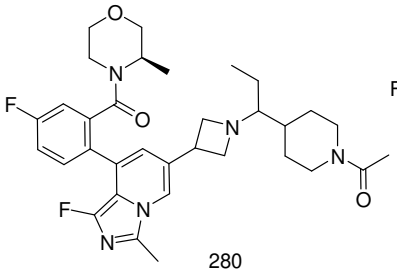

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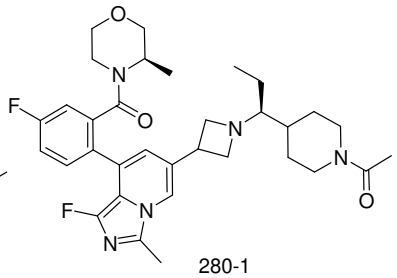

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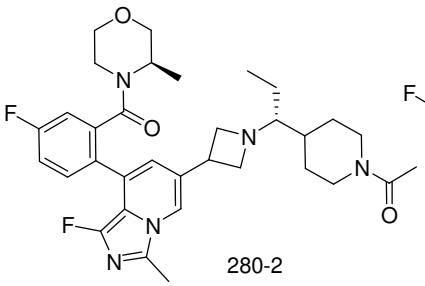

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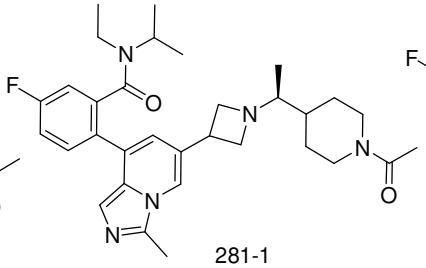

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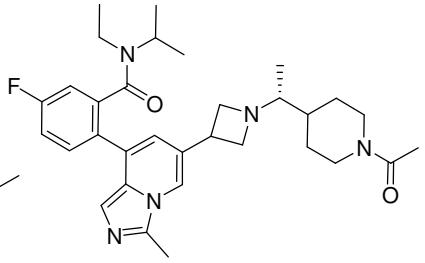

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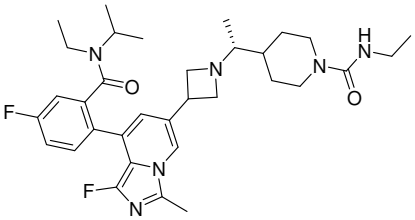

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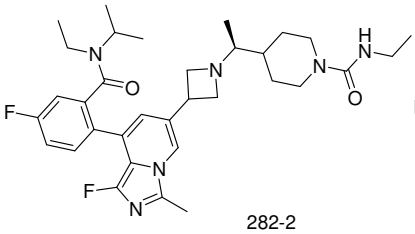

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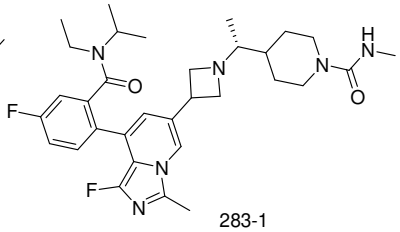

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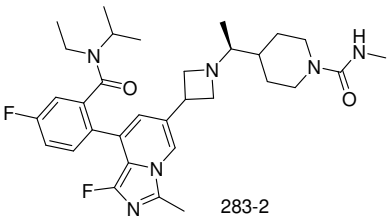

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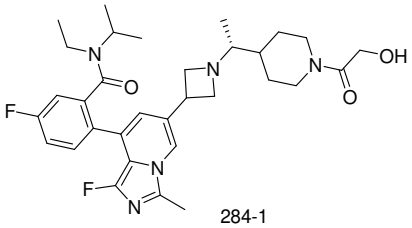

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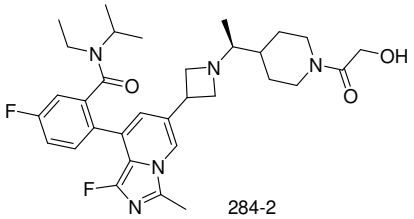

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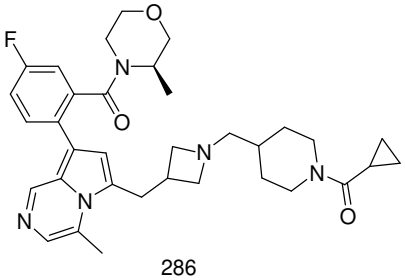

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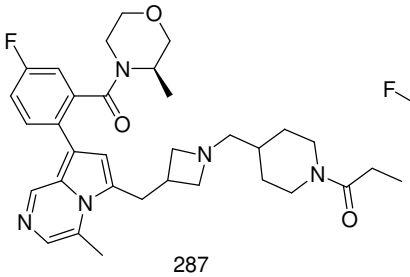

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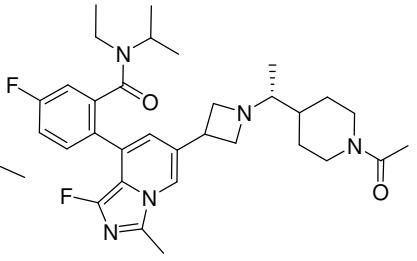

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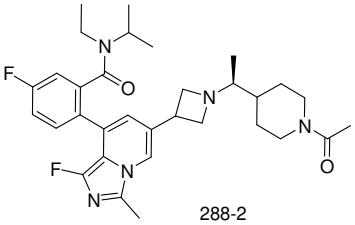

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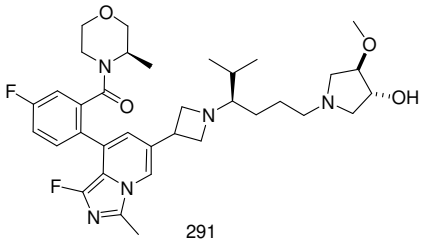

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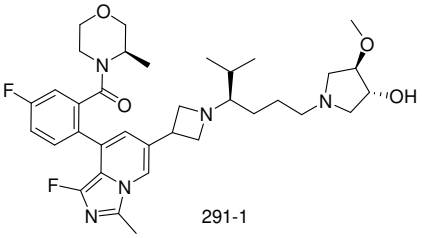

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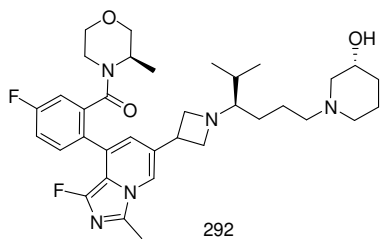

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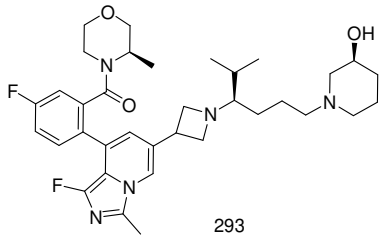

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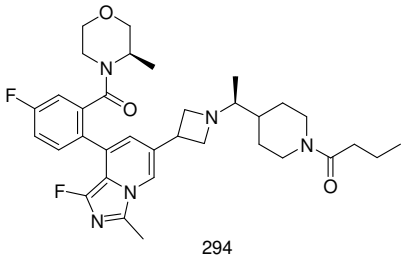

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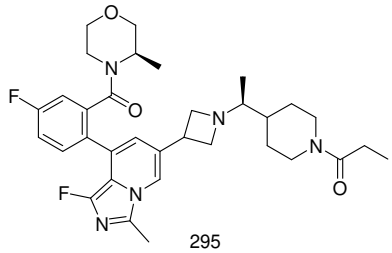

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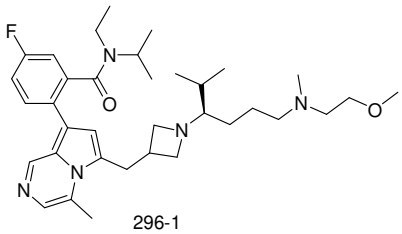
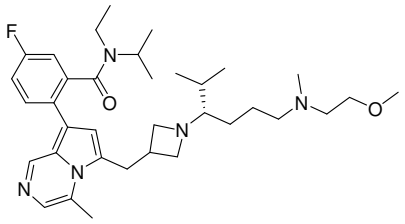
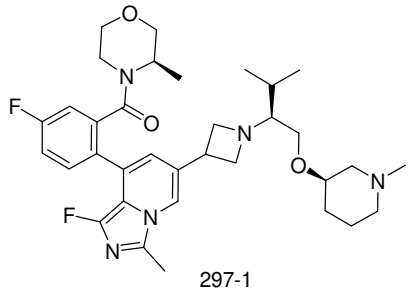


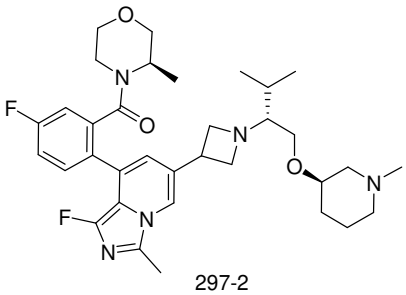
296-1



296-2



297-1



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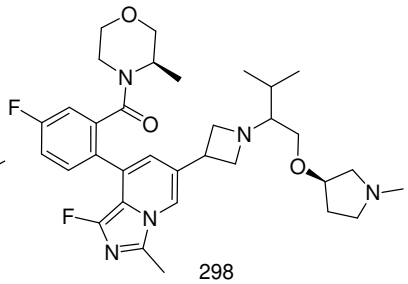

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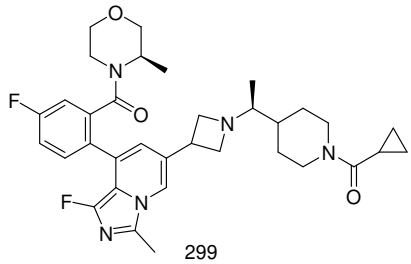

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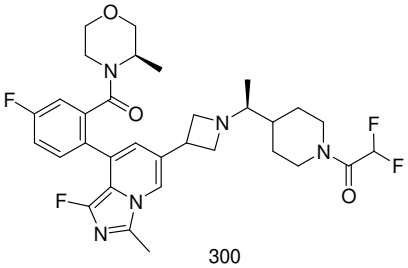

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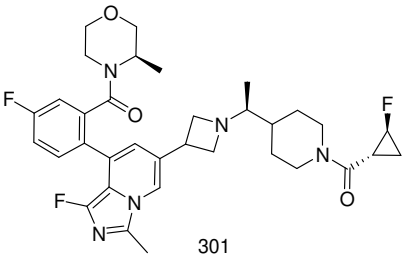

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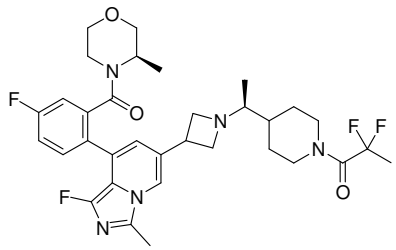

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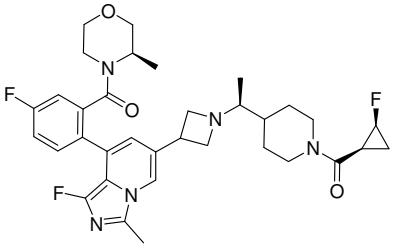

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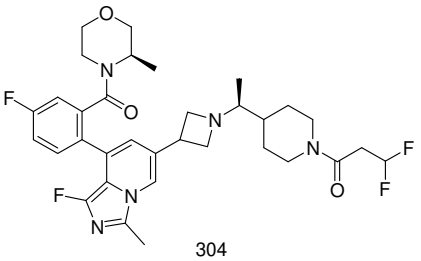

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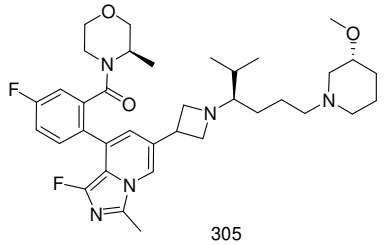

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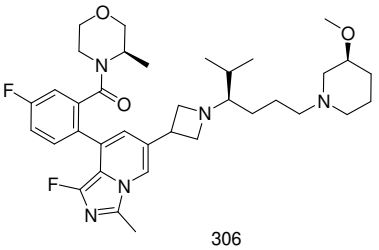

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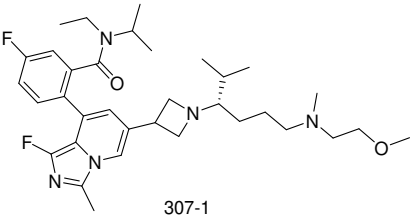
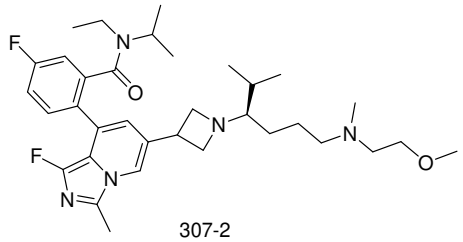


307-1



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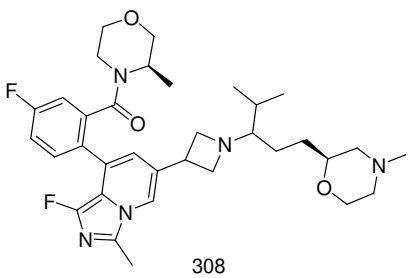

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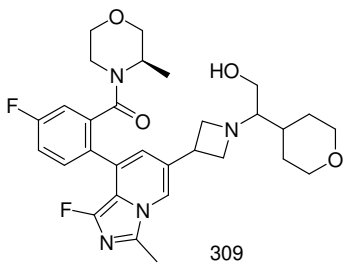

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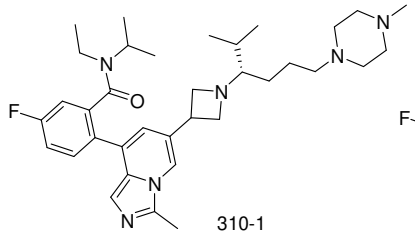

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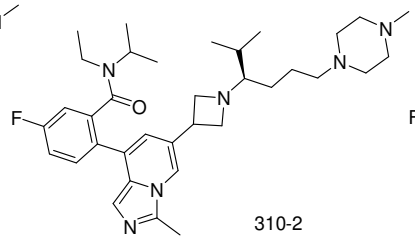

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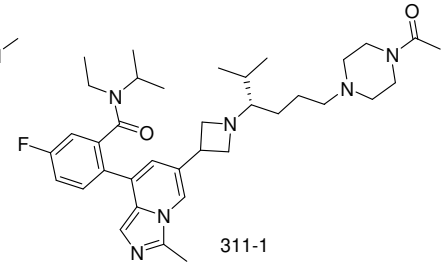

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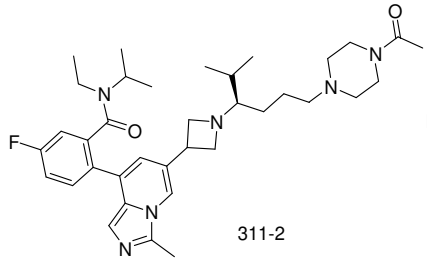

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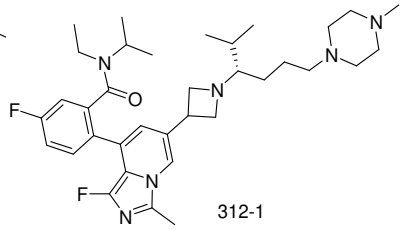

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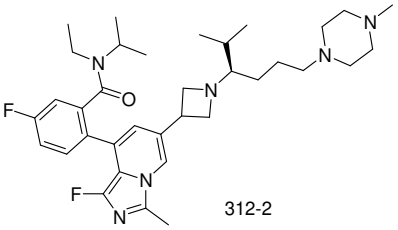

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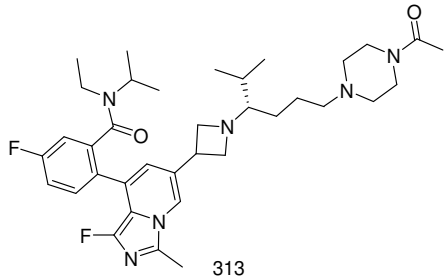

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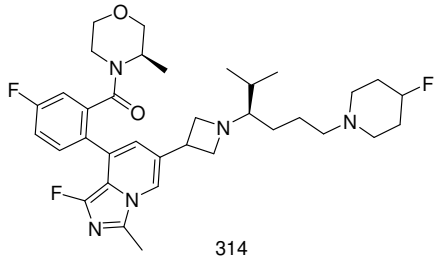

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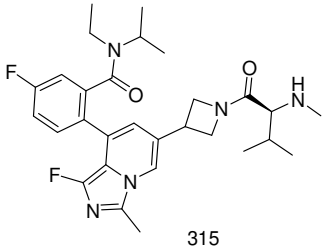

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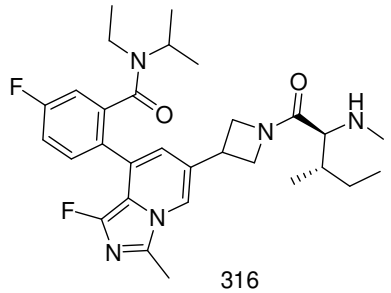

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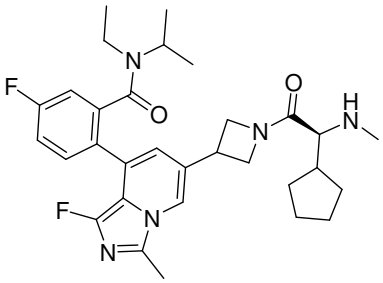

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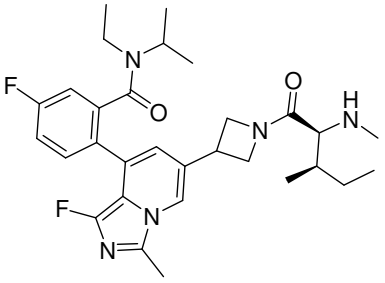

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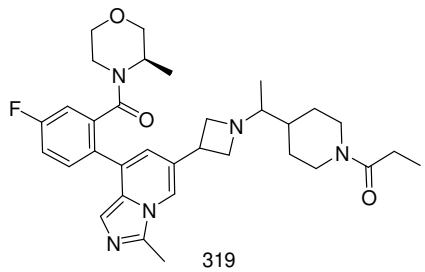

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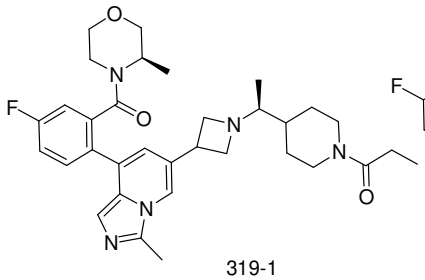

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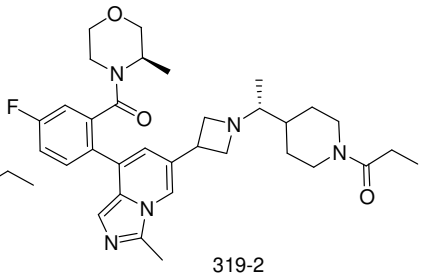

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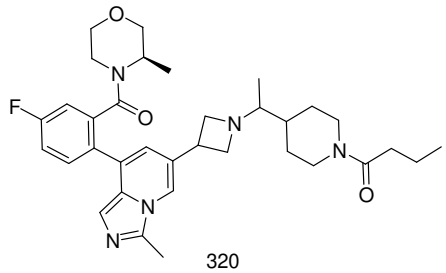

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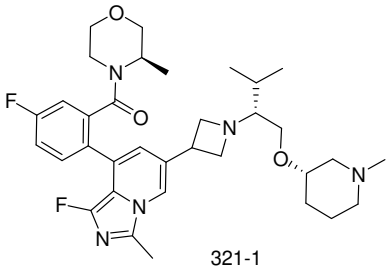

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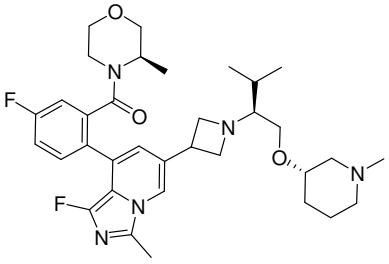

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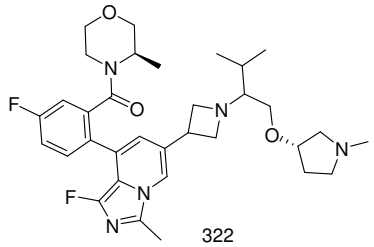

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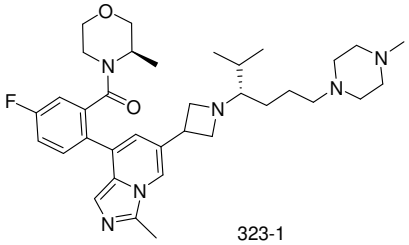

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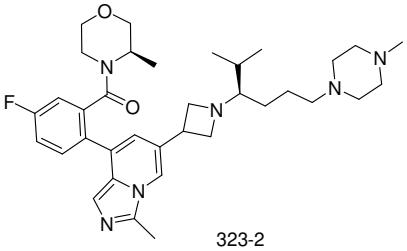

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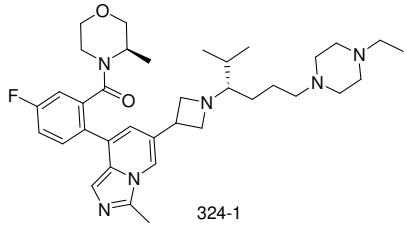

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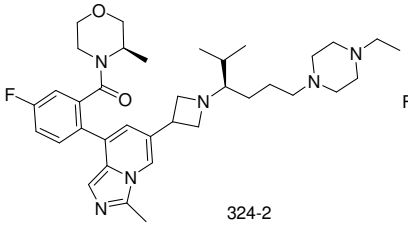

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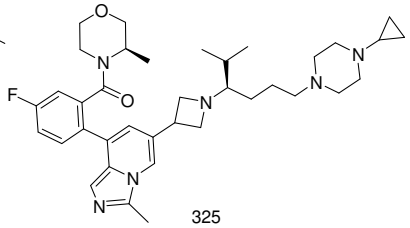

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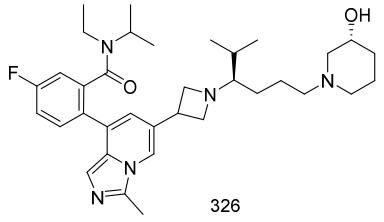

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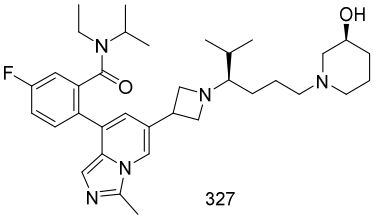

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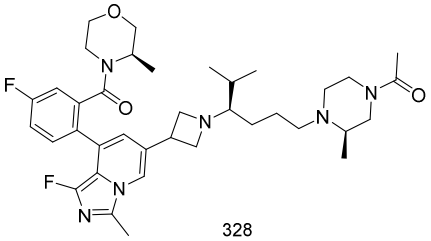

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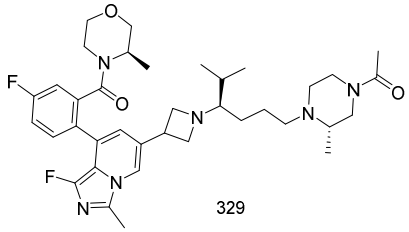

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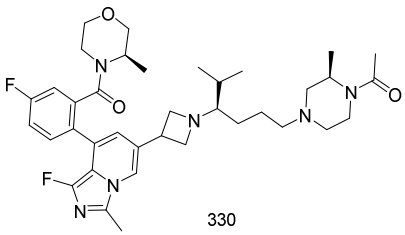

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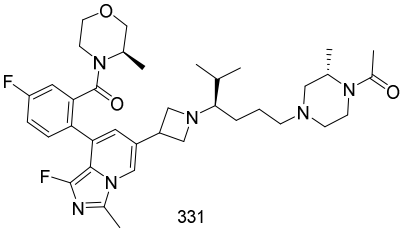

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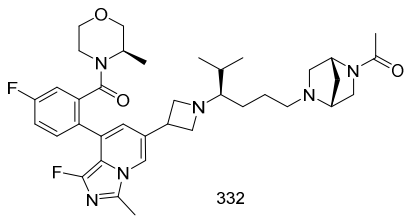
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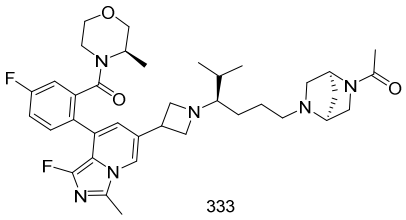
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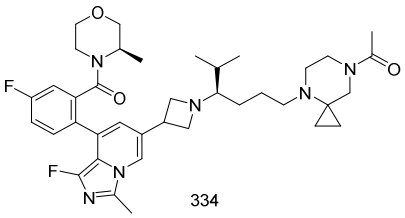
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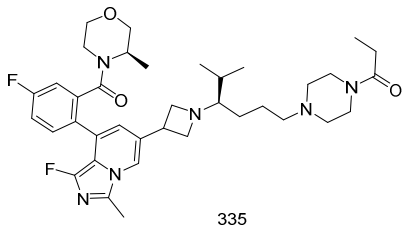
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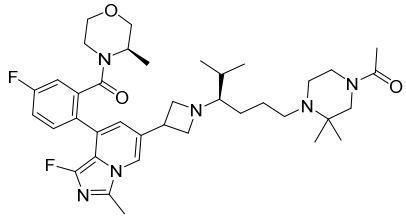
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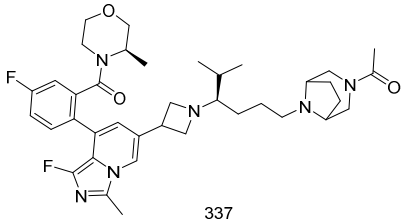
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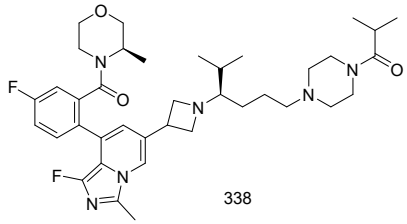
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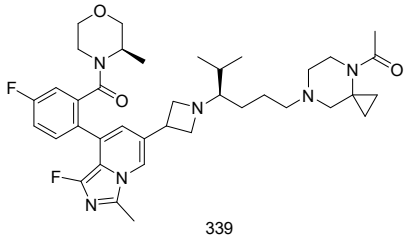
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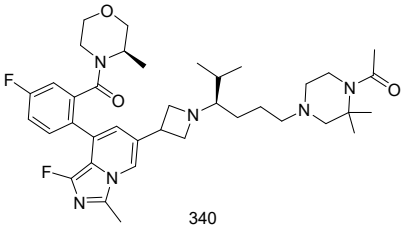
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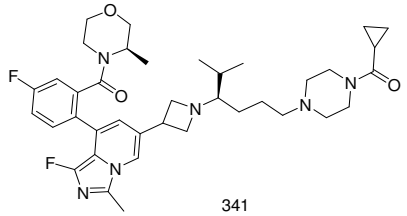
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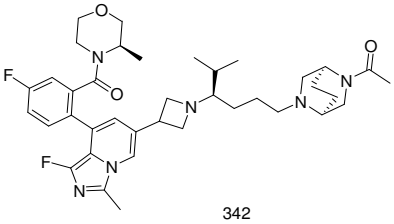
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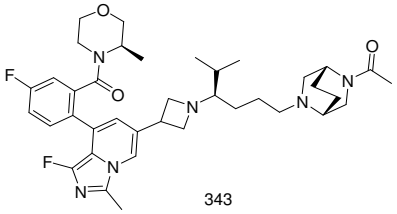
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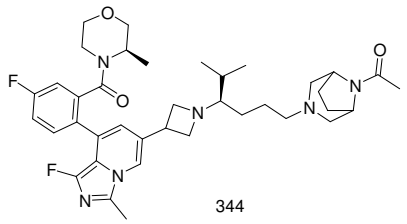
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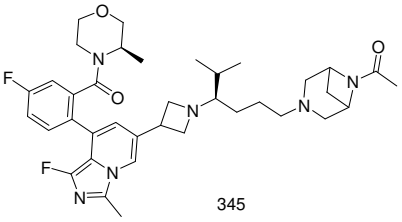
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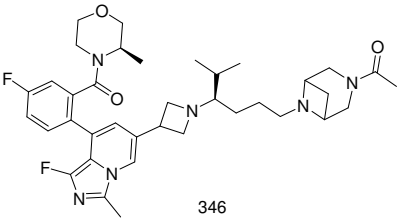
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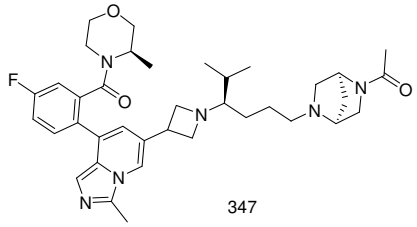
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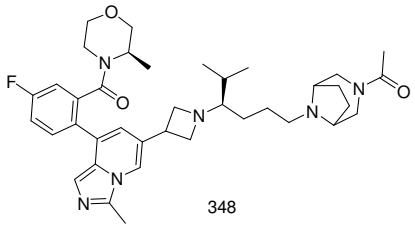
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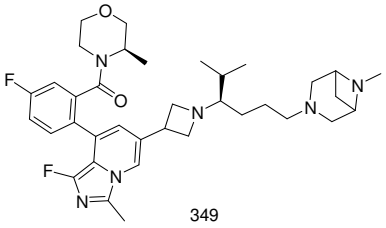
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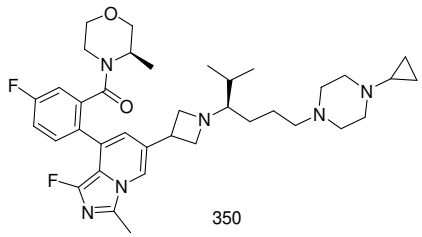
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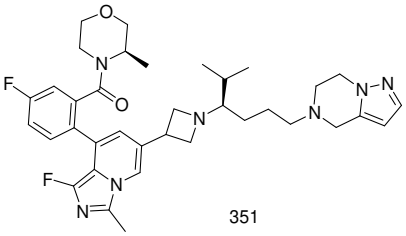
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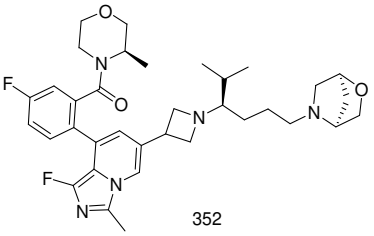
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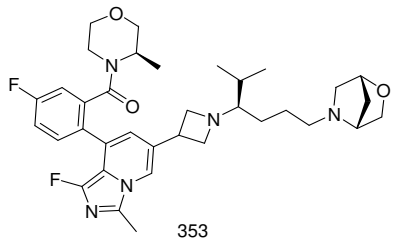

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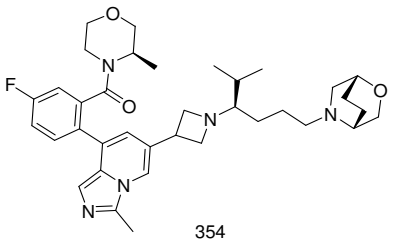

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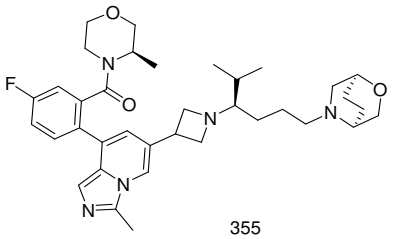

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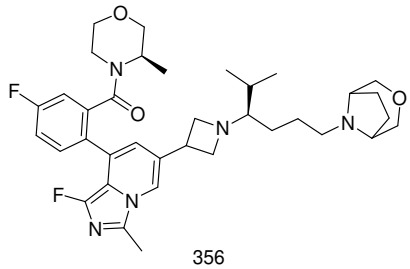

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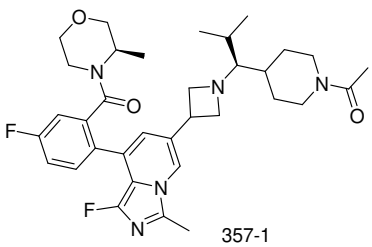

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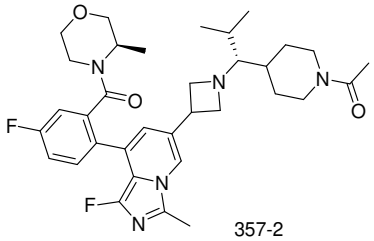

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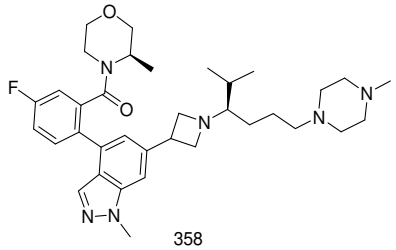

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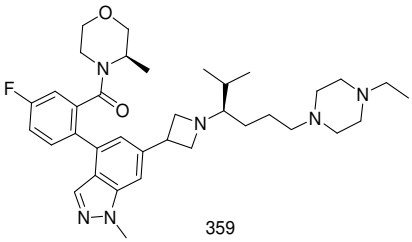

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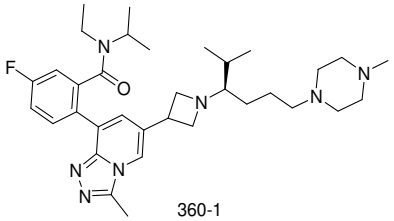

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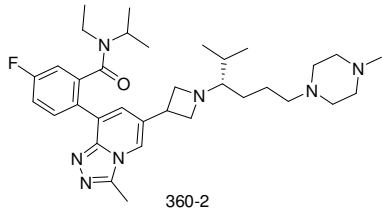

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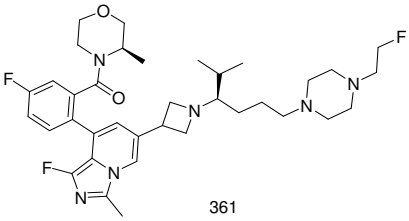

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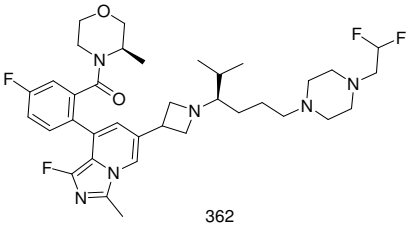

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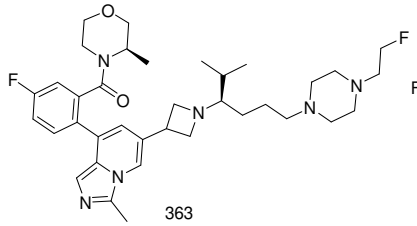

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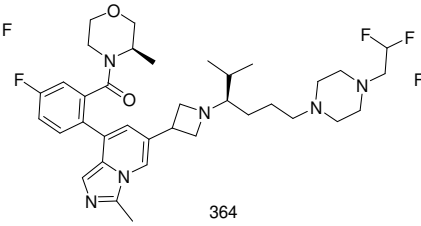

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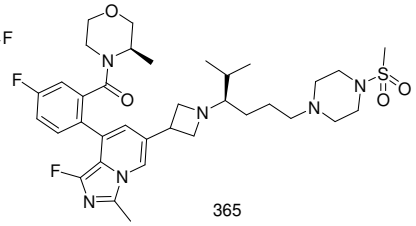

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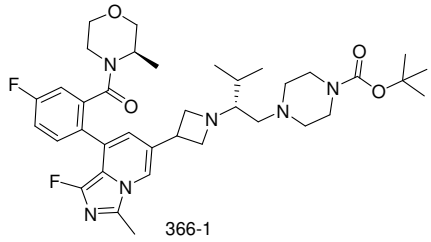

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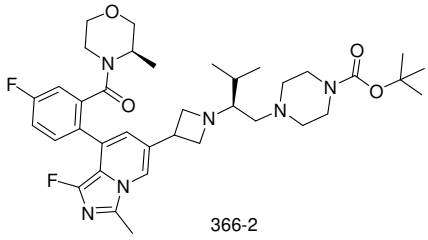

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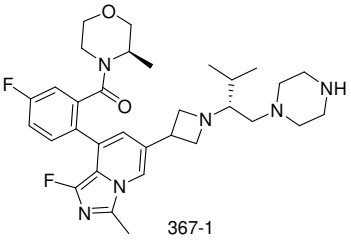

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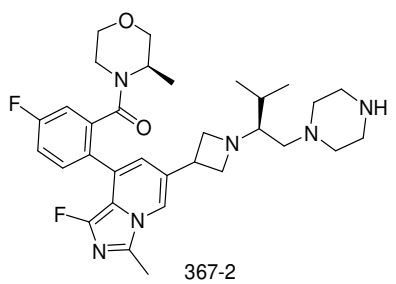

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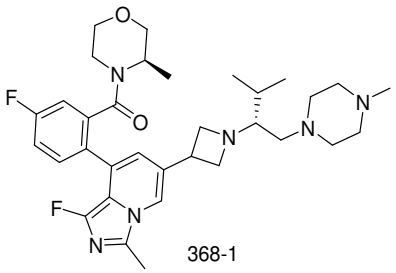

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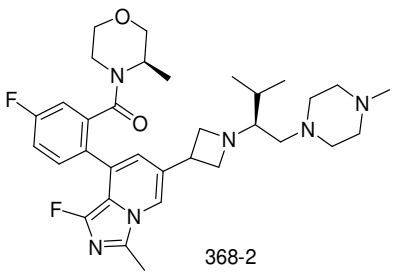

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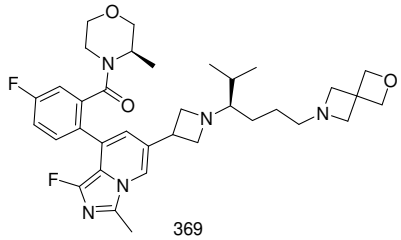

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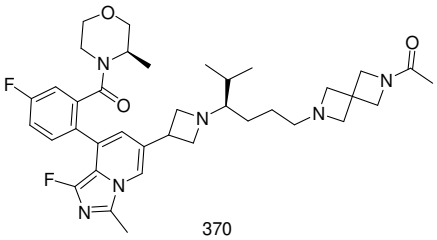

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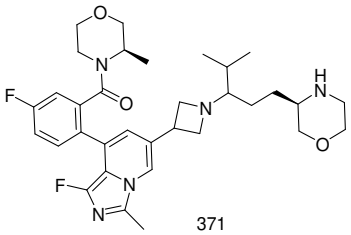

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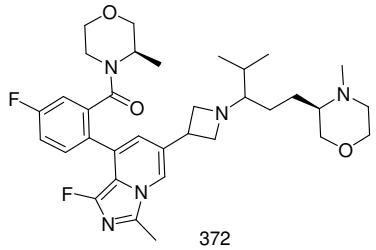

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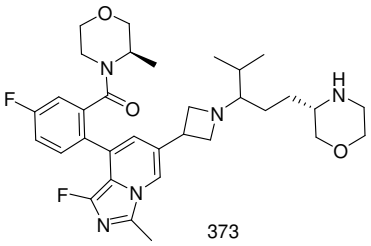

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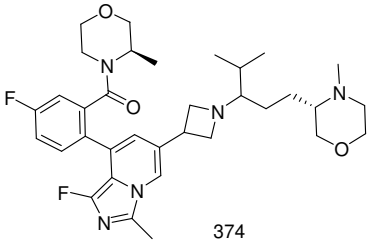

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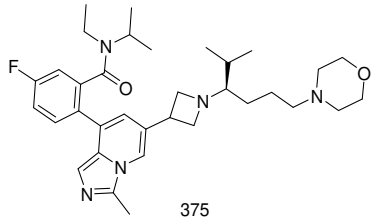

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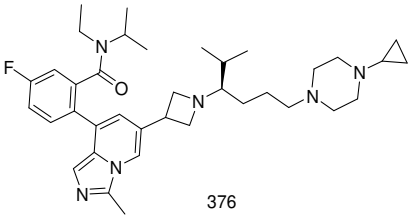

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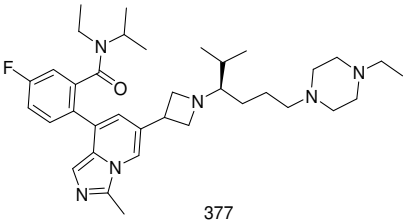

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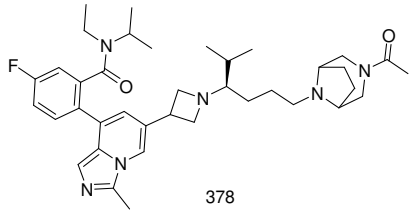

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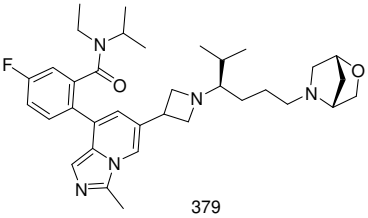

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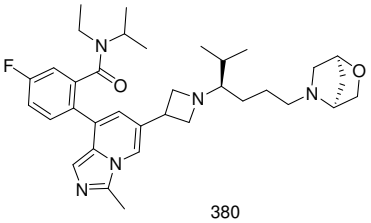

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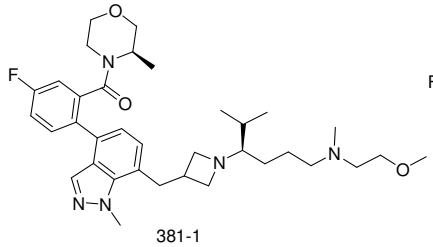

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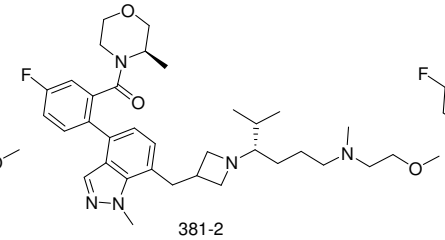

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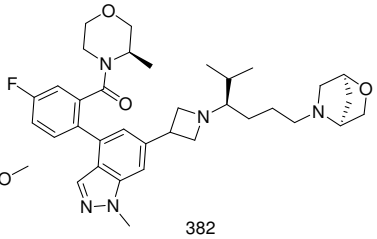

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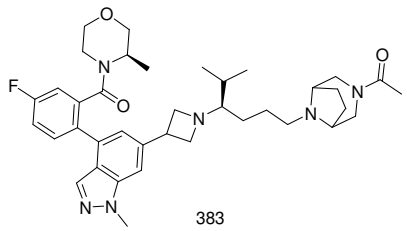

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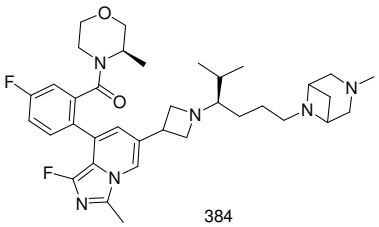

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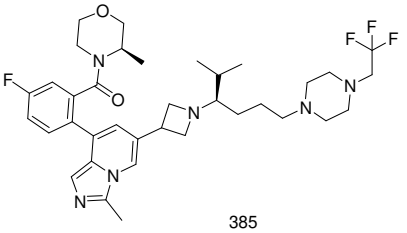

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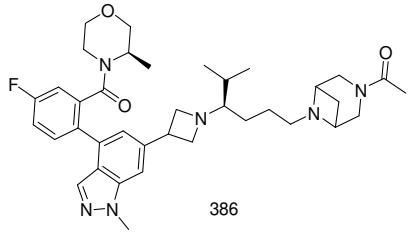

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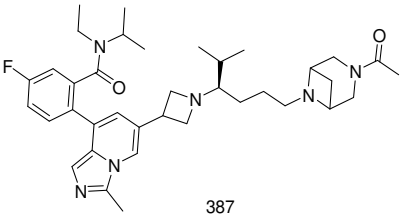

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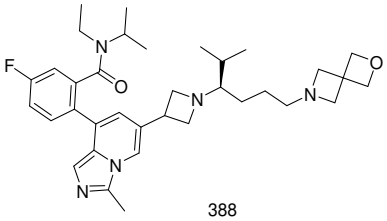

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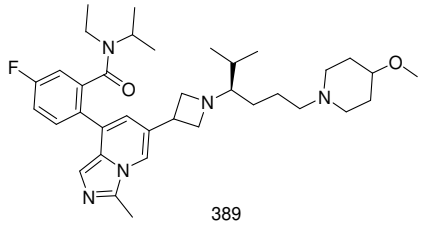

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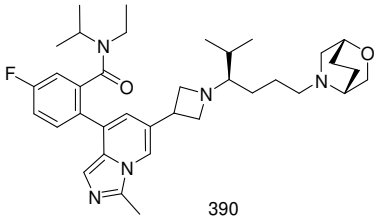

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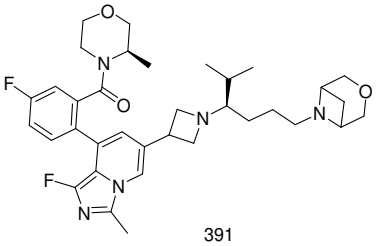

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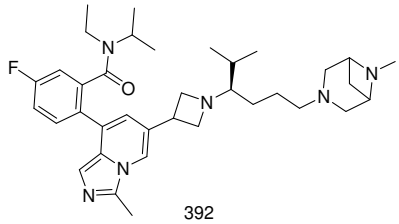

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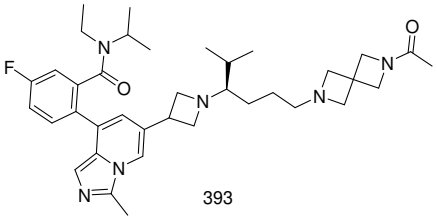

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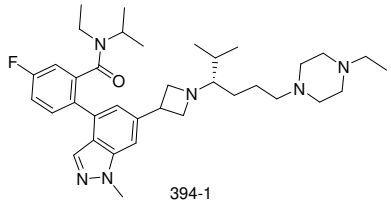

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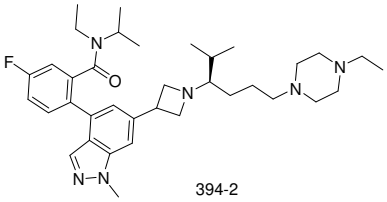
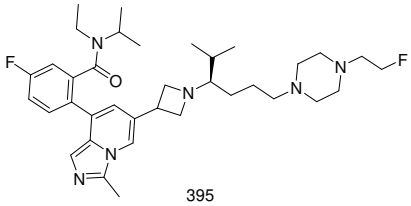


394-2



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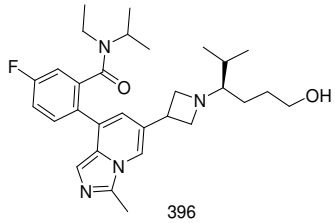

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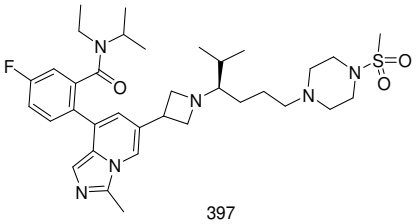

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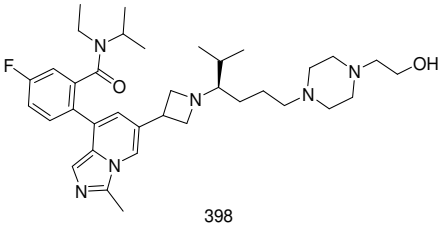

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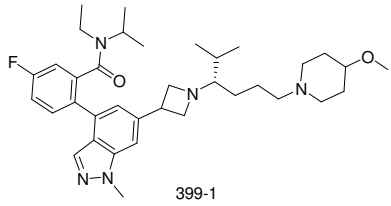
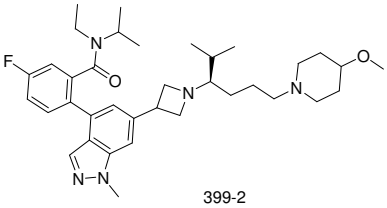


399-1



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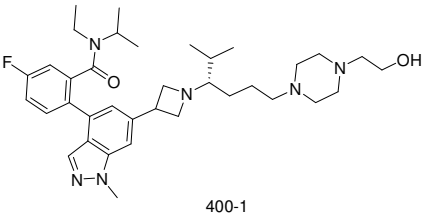

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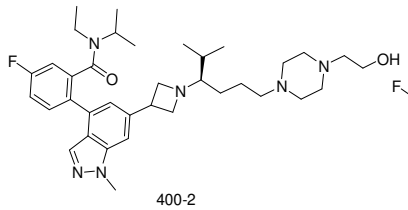

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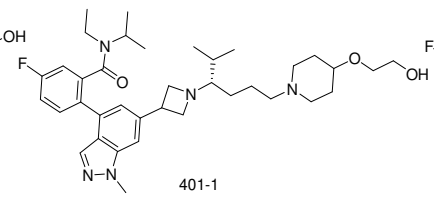

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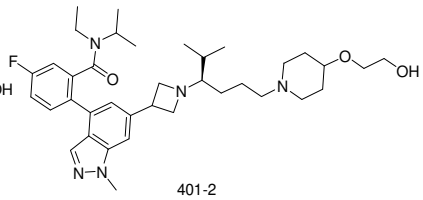

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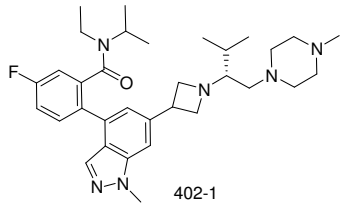

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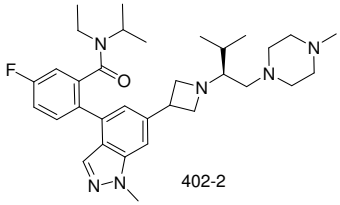

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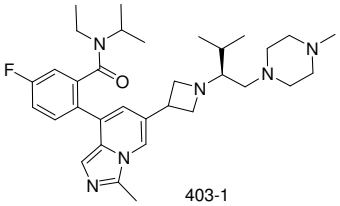

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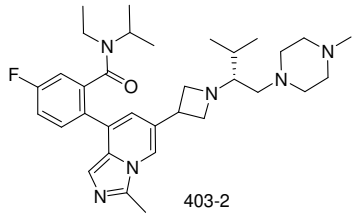

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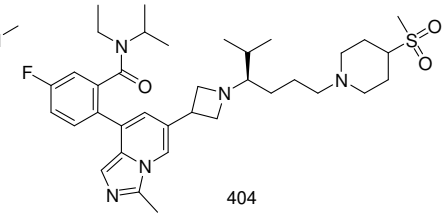

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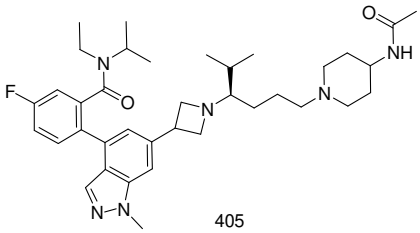

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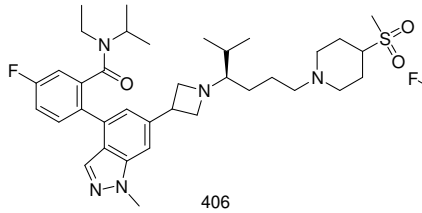

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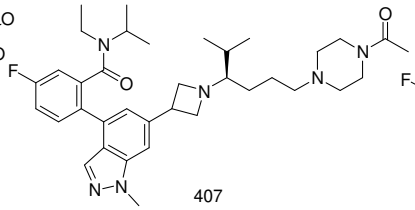

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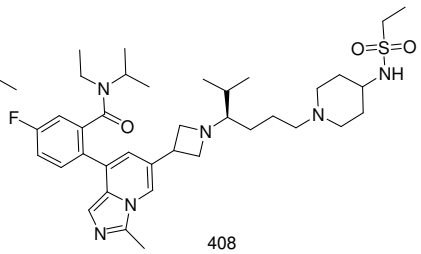

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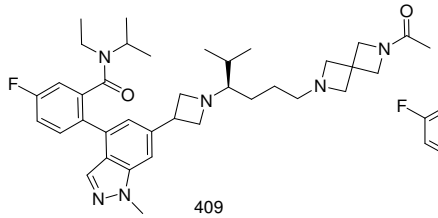

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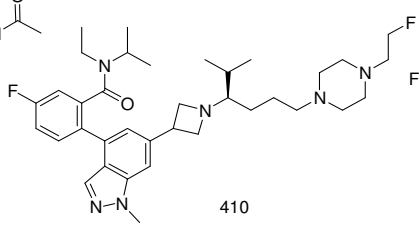

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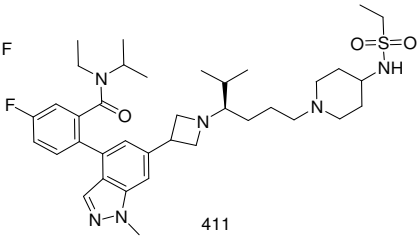

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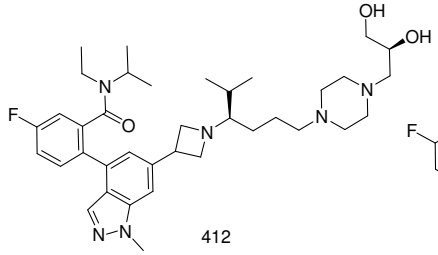

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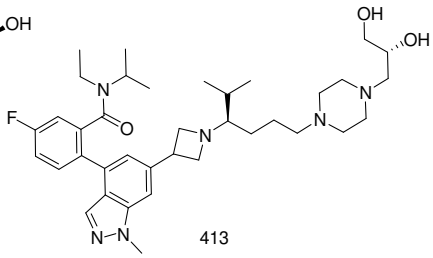

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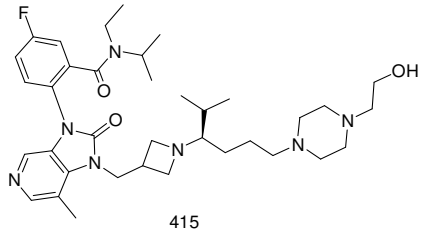

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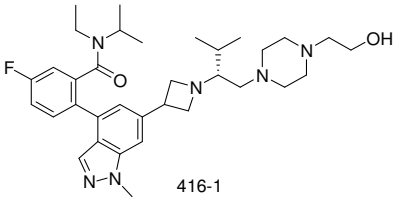

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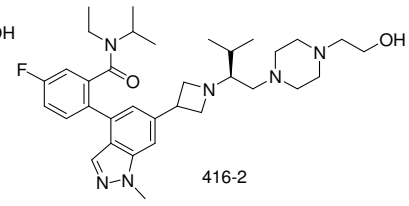

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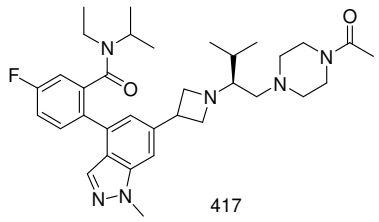

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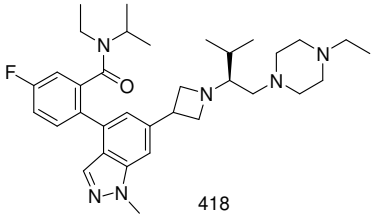

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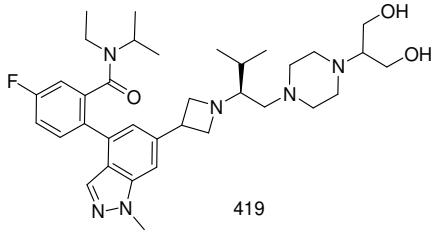

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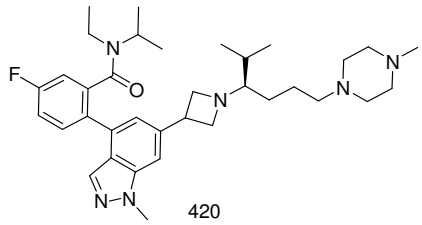

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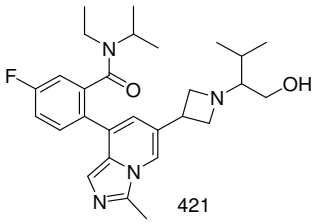

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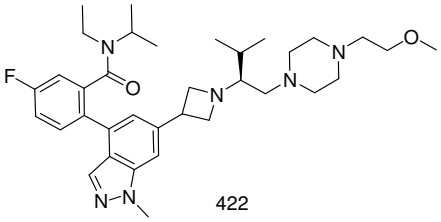

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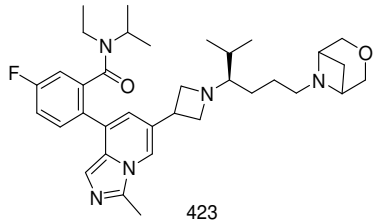

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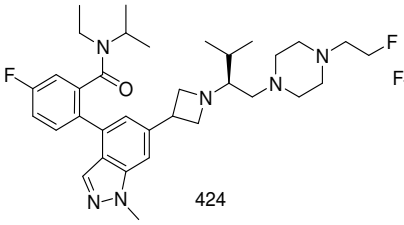

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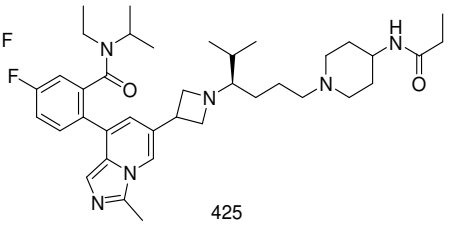

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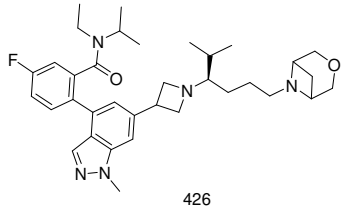

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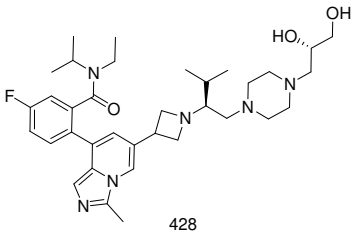

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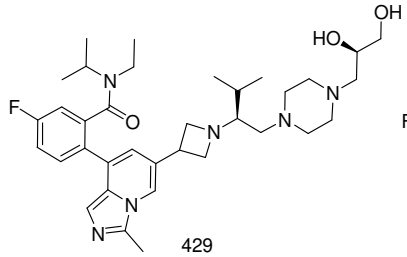

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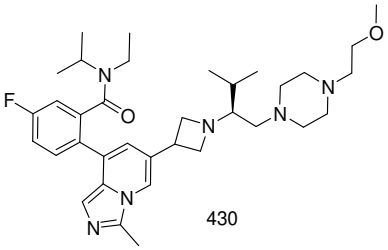

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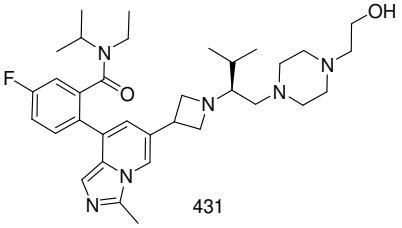

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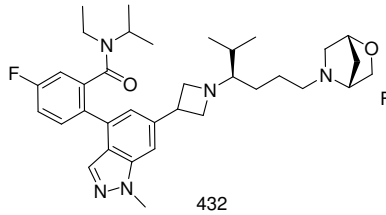

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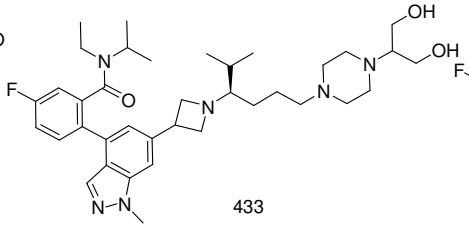

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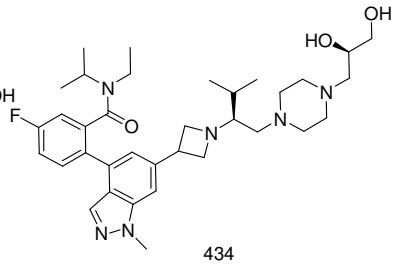

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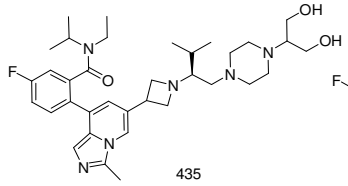

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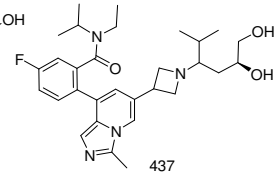

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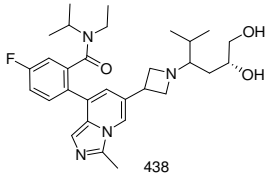

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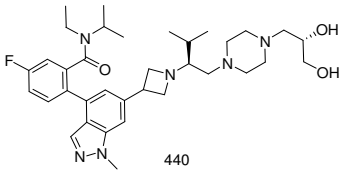

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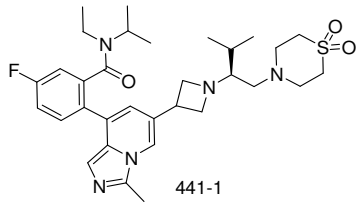

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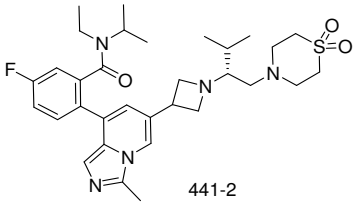

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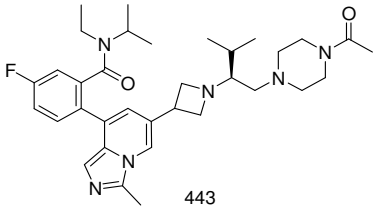

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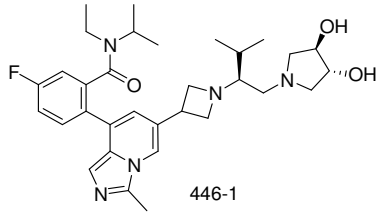

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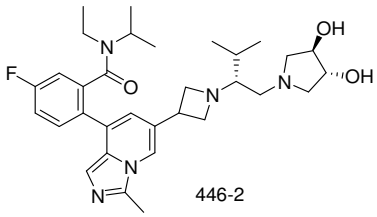

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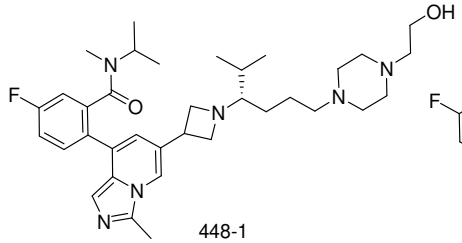

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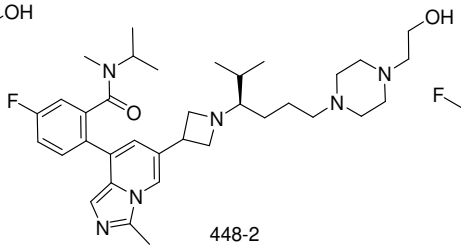

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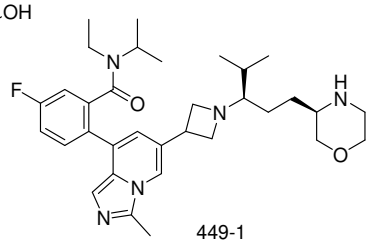

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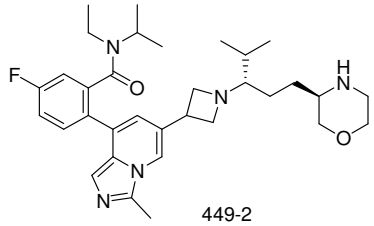

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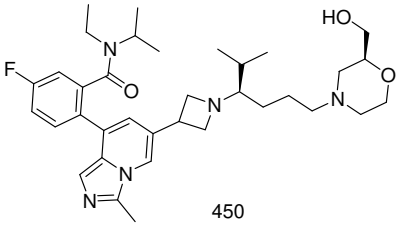

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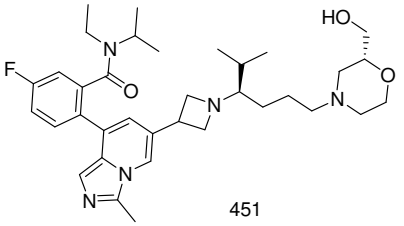

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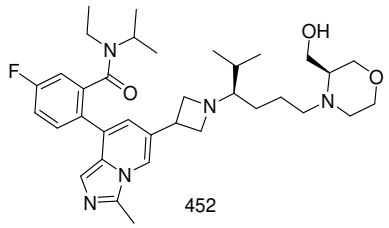

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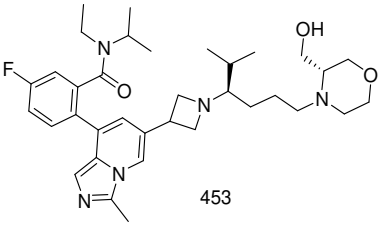

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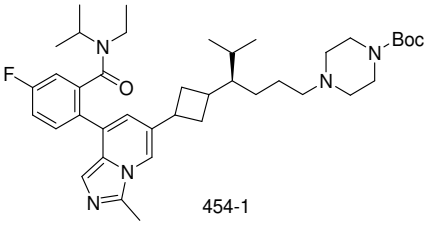
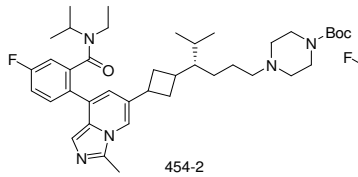


454-1



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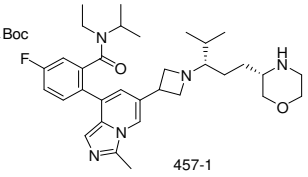

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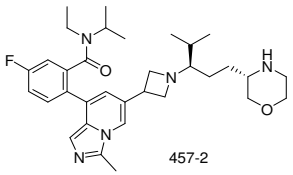

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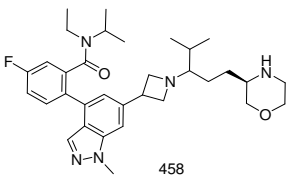

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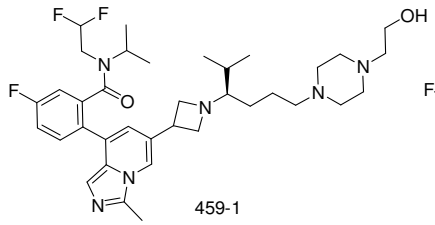

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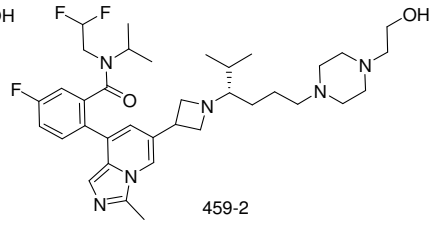

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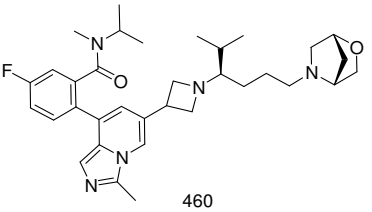

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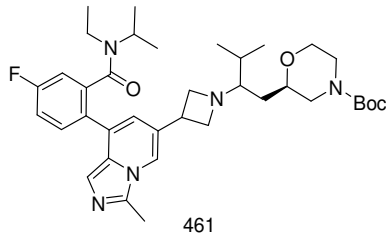

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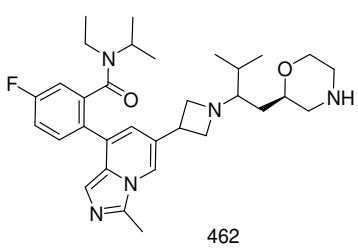

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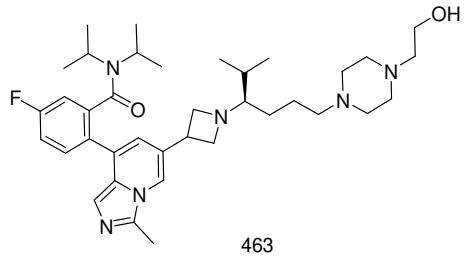

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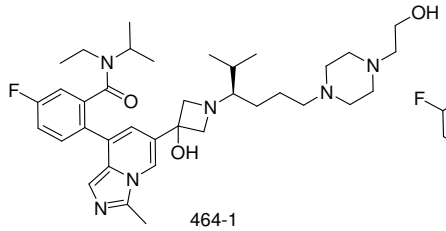

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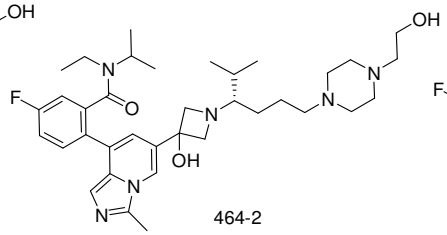

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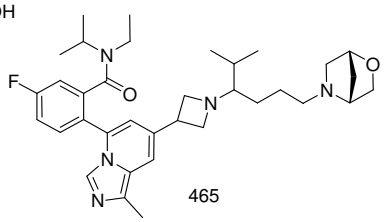

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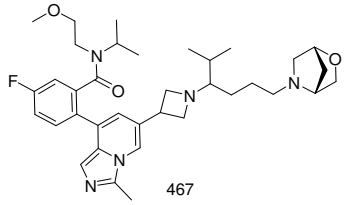

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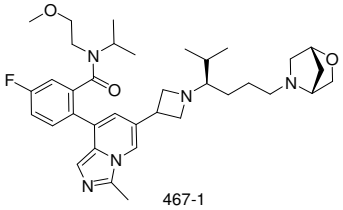

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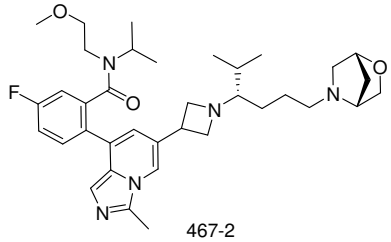

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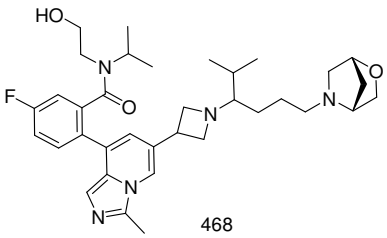

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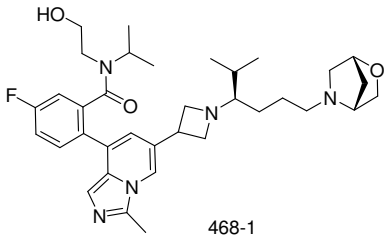

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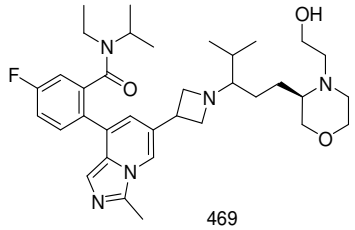

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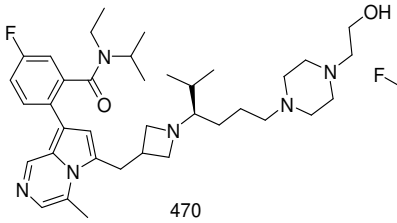

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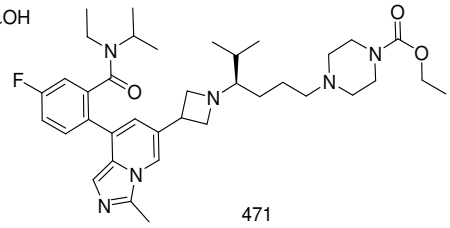

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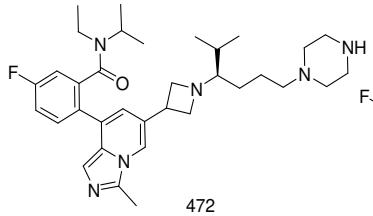

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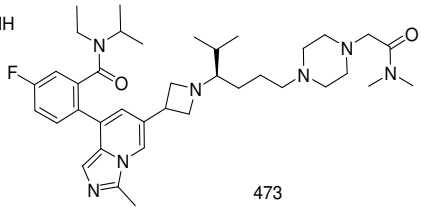

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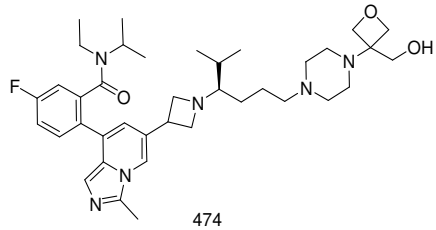

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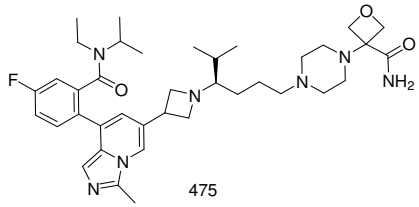

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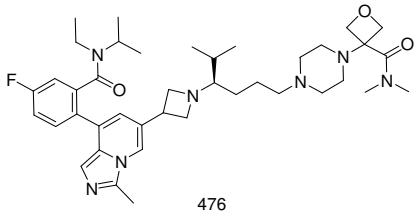

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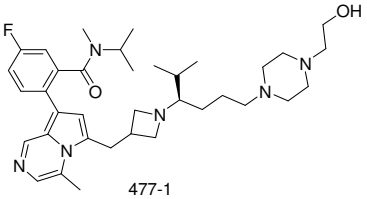

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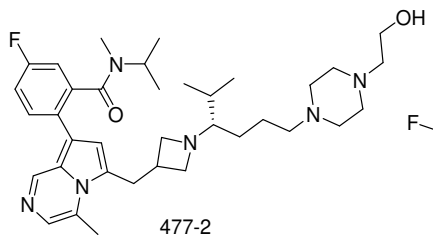

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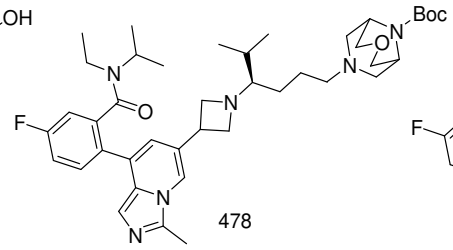

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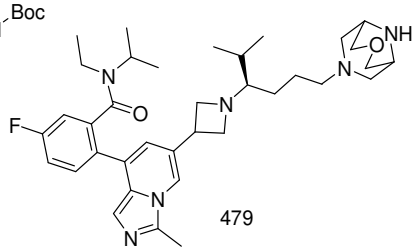

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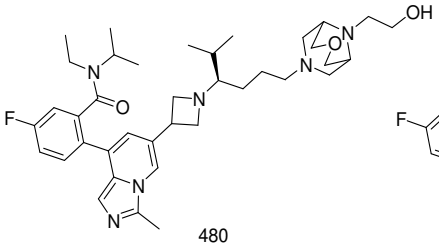

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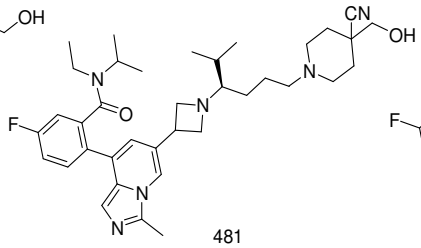

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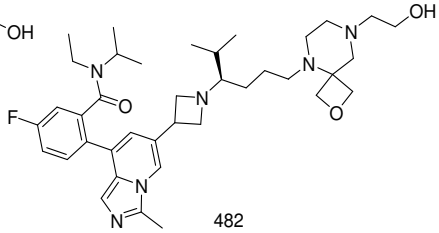

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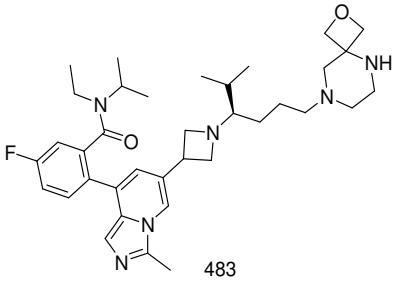

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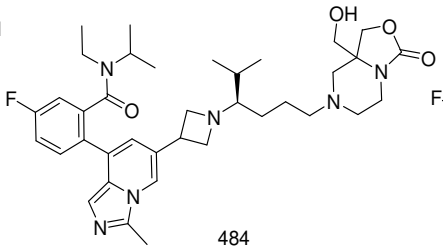

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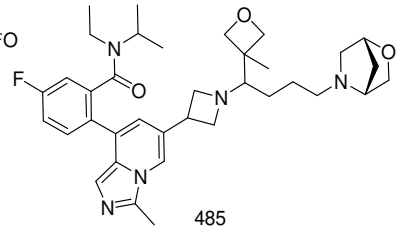

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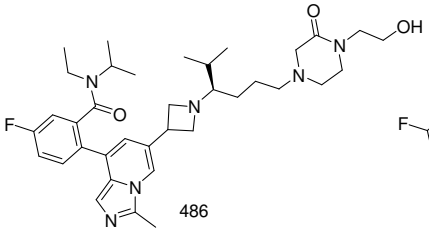

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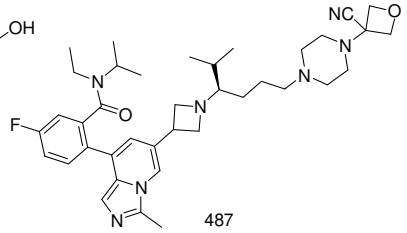

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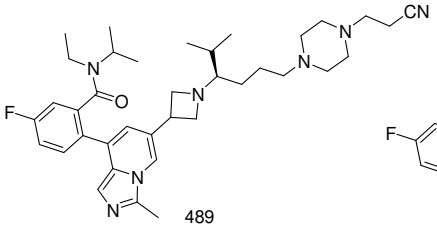

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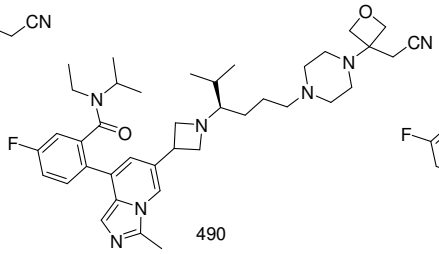

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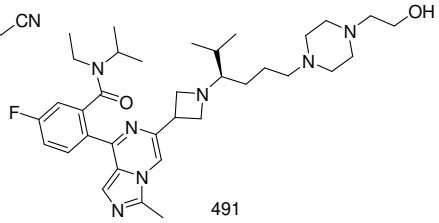

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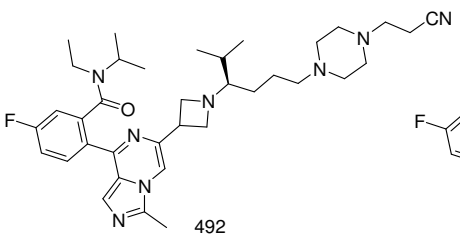

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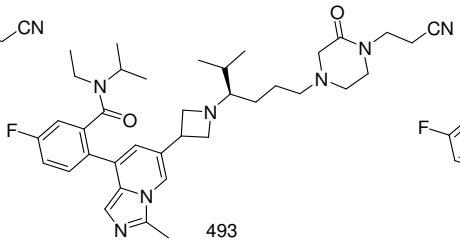

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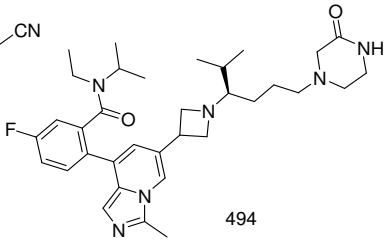

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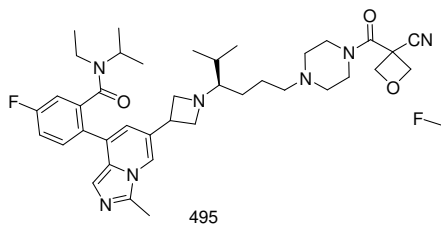

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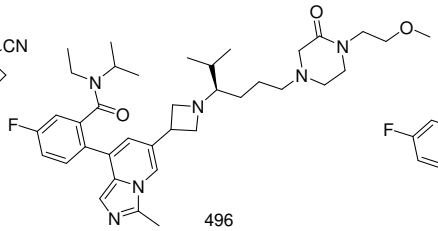

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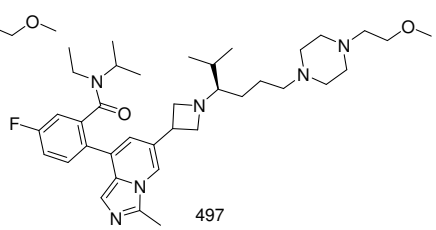

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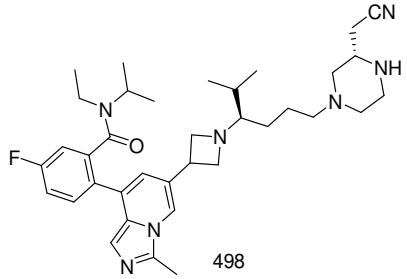

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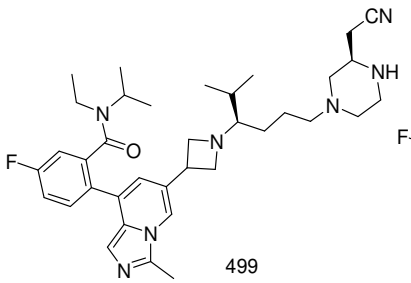

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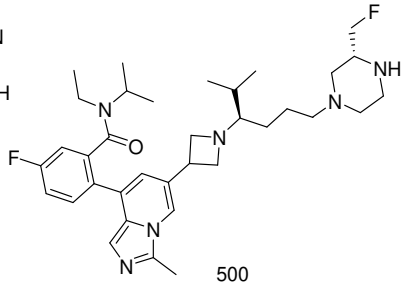

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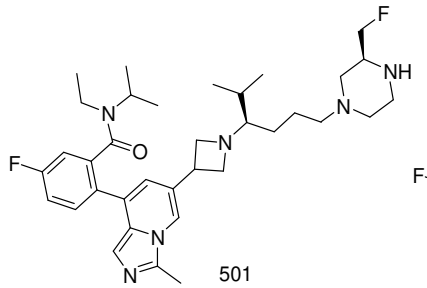

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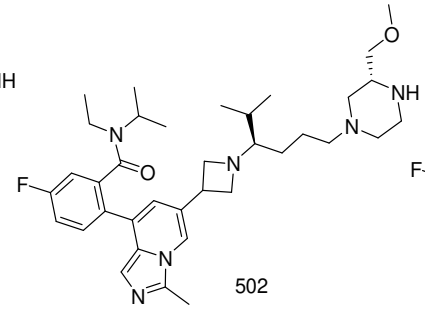

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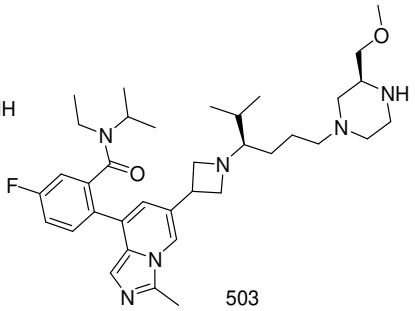

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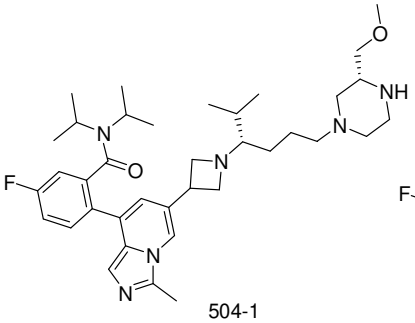

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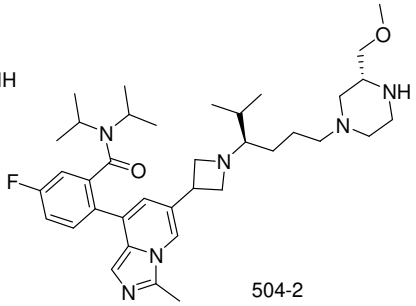

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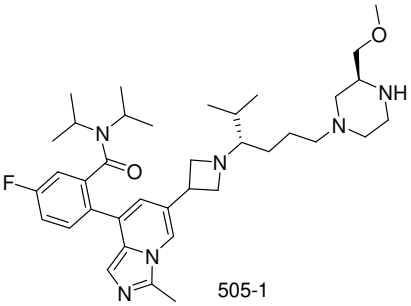

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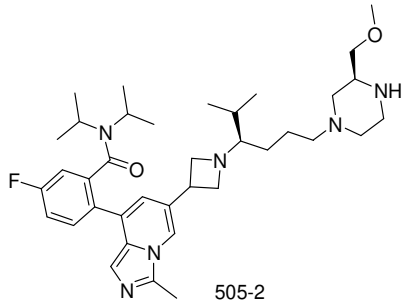
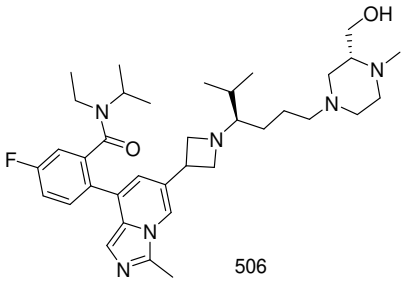


505-2



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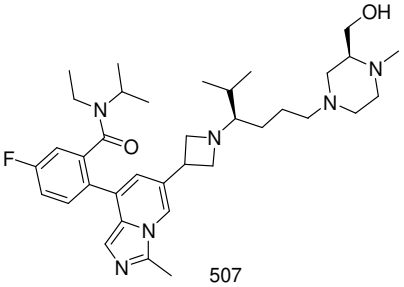

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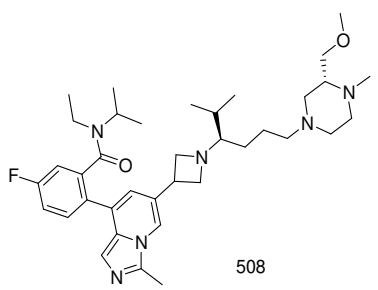
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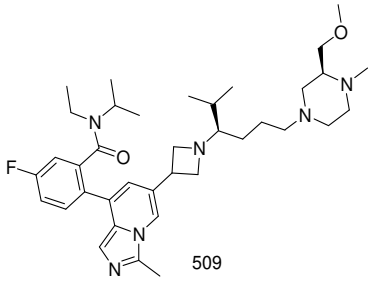
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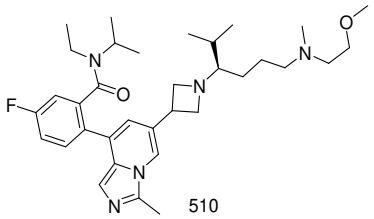
510

19.A pharmaceutical composition, comprising the compound according to any one of claims 1 to 18 or a pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof, and a pharmaceutically acceptable excipient.

20.Use of the compound according to any one of claims 1 to 18 or a pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof in the preparation of a medicament for inhibiting Menin-MLL interaction.

21.Use of the compound according to any one of claims 1 to 18 or a pharmaceutically acceptable salt, stereoisomer, ester, prodrug, solvate and deuterated compound thereof in the preparation of a medicament for preventing and/or treating a disease mediated by Menin-MLL interaction;

preferably, said diseases is selected from the group consisting of: a tumor, diabetes, insulin resistance, hyperglycemia, an autoimmune disease and non-alcoholic hepatitis; and

more preferably, said tumor is a hematological tumor.