HETEROCYCLIC SUBSTITUTED PYRIMIDOPYRAN COMPOUNDS AND THEIR APPLICATIONS

RELATED APPLICATIONS

This application claims the benefit of and priority to International Patent Application No. PCT/CN2024/083328, filed on March 22, 2024, and the benefit of and priority to Chinese Application No 202410309827.4, filed on March 18, 2024, the contents of which are incorporated herein by reference in their entirety, wherein, the International Patent Application No PCT/CN2024/083328 claims the benefit of and priority to Chinese Application Nos. 202310290481.3, filed March 23, 2023, 202311634664.9, filed November 30, 2023, and 202410309827.4, filed March 18, 2024, the contents of which are incorporated herein by reference in their entirety.

Technical Field

The present disclosure is directed to a class of piperazine bridging ring substituted pyrimidopyran compounds and their applications, in particular to compounds of Formula (I"), Formula (I'), or Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof.

BACKGROUND

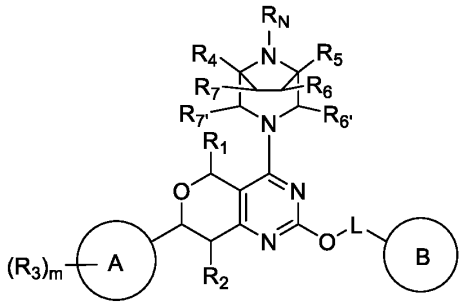
KRAS is the most common oncogenic mutation gene, and KRAS mutations occur in about 1 in 7 cancers. KRAS mutation/KRAS amplification is most common in colorectal cancer (US: ~45% China: ~49%), pancreatic cancer (US: ~90% China: ~87% non-small cell lung cancer (US: ~35% China: ~13%). Among them, $KRAS^{G12D}$, $KRAS^{G12V}$ and $KRAS^{G12C}$ account for the largest proportion. KRAS is a murine sarcoma virus oncogene and an important member of the RAS protein. KRAS acts as a molecular switch that regulates the path of cell growth when its function is normal; after KRAS gene mutation, it can independently transmit growth and proliferation signals to downstream pathways independent of upstream growth factor receptor signals, resulting in uncontrolled cell growth and tumor progression. At the same time, whether the KRAS gene is mutated is also an important indicator of tumor prognosis.

At present, small molecules that directly target KRAS mutations are mainly concentrated in the field of $KRAS^{G12C}$. Among them, Amgen's AMG510 and Mirati Therapeutics' MRTX849 have both been approved for marketing, and have shown good therapeutic effects in patients with $KRAS^{G12C}$-mutant tumors. MRTX1133, as a small molecule drug targeting $KRAS^{G12D}$ mutation, has entered clinical phase I, and it has shown excellent anti-tumor properties in preclinical studies. However, there are still some problems with this class of compounds. Tumor patients with $KRAS^{G12D}$ mutations have not yet benefited from precision medicine, and the continued development of small molecule inhibitors targeting $KRAS^{G12D}$ is still of great significance.

A series of small molecule inhibitors targeting $KRAS^{G12D}$ and methods of making the same are disclosed.

SUMMARY

In certain aspects, the present disclosure provides a compound of formula (I''):



(I''),

or a stereoisomer thereof, or pharmaceutically acceptable salt thereof, wherein each of the variable in Formula (I'') is described, embodied, and exemplified herein.

In certain aspects, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof, comprising administering to the subject a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof (e.g., in a therapeutically effective amount).

In certain aspects, the present disclosure provides methods of treating a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof, comprising administering to the subject a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof (e.g., in a therapeutically effective amount).

In certain aspects, the present disclosure provides uses of a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

In certain aspects, the present disclosure provides uses of a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

In certain aspects, the present disclosure provides compounds disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

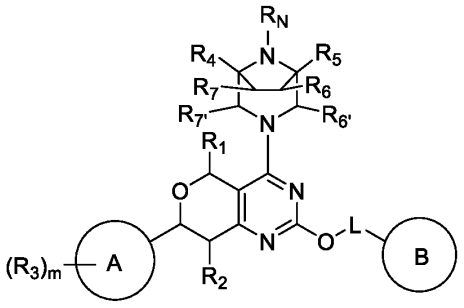
In certain aspects, the present disclosure provides compounds disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

DETAILED DESCRIPTION

The present disclosure relates to compounds and compositions that are useful as pan-KRAS inhibitors. The present disclosure also relates to methods of treating a disease or disorder in a subject in need thereof by administering (e.g., in a therapeutically effective amount) a compound disclosed herein. The present disclosure further relates to methods of treating a disease or disorder in a subject in need thereof, comprising administering (e.g., in a therapeutically effective amount) a pharmaceutical composition comprising a compound disclosed herein.

Compounds of the Application

In certain aspects, the present disclosure provides a compound of Formula (I''):



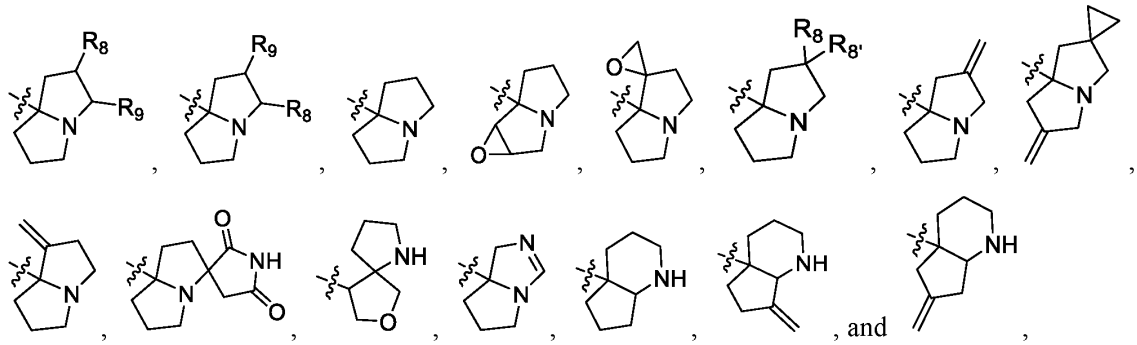
(I''),

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

R_N is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 F or Cl;

Ring A is selected from C_6 aryl and 5-6 membered heteroaryl;

Ring B is selected from



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is -C($R_{L1}R_{L2}$)-, wherein R_{L1} and R_{L2} are each independently selected from H, D, and C_{1-3} alkyl;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, -C(=O)-R_d, -C(=O)-$NR_{b1}R_{b2}$, and =NO(C_{1-3} alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and -C(=O)-$NR_{b1}R_{b2}$;

R_8 is selected from H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or, R_8 and $R_{8'}$ together with the carbon atom to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the C_{3-5} cycloalkyl and 3-5 membered heterocyclyl are each independently optionally substituted with 1, 2, or 3 R_{10};

R_9 is selected from -C(=O)-$NR_{b3}R_{b4}$ and -CH_2R_c;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, -C(=O)-R_d, -S-R_d, -S(=O)-R_d, -S(=O)$_2$-R_d, -NH-C(=O)-R_d, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F, and the C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally

substituted with 1, 2, 3, 4, or 5 R_{s1};

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, or 4 R_{e1};

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{e1};

R_{b3} and R_{b4} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, or 4 R_{e2};

or, R_{b3} and R_{b4} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{e2};

R_c is selected from F, Cl, Br, I, OH, NH_2, $-(C=O)NR_{C1}R_{C2}$, $-O(C=O)NR_{C1}R_{C2}$, $-NR_{C0}(C=O)R_{C1}$, and $-NR_{C0}(C=O)NR_{C1}R_{C2}$;

R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

R_d is C_{1-3} alkyl;

R_{e1} is selected from F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, $-S(=O)_2-(C_{1-3}$ alkyl), $-(C=O)(C_{1-3}$ alkyl), $-(C=O)O(C_{1-3}$ alkyl), $-(C=O)NH(C_{1-3}$ alkyl), $-(C=O)N(C_{1-3}$ alkyl$)_2$, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl;

R_{e2} is selected from F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, $-S(=O)_2-(C_{1-3}$ alkyl), $-(C=O)(C_{1-3}$ alkyl), $-(C=O)O(C_{1-3}$ alkyl), $-(C=O)NH(C_{1-3}$ alkyl), $-(C=O)N(C_{1-3}$ alkyl$)_2$, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}, and wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2};

or, two R_{e2} together with the carbon atoms to which they are attached form a C_6 aryl or 5- or 6-membered heteroaryl;

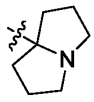
R_{s1} is selected from oxo, F, Cl, Br, I, OH, NH_2, NO_2, C_{1-6} alkyl, C_{1-6} alkylamino, di-C_{1-6} alkylamino, CN, C_{1-6} alkoxy, $-S(=O)_2-(C_{1-3}$ alkyl), $-(C=O)(C_{1-3}$ alkyl), $-(C=O)O(C_{1-3}$ alkyl), $-(C=O)NH(C_{1-3}$ alkyl), and $-(C=O)N(C_{1-3}$ alkyl$)_2$;

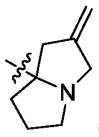
R_{s2} is selected from F, Cl, Br, I, OH, NH_2, C_{1-6} alkylamino, di-C_{1-6} alkylamino, CN, C_{1-6} alkoxy,

-S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), and -(C=O)N(C_{1-3} alkyl)$_2$; and

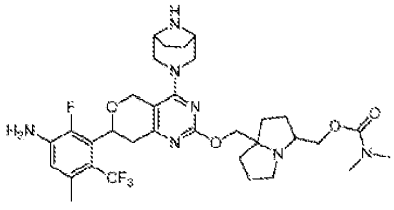
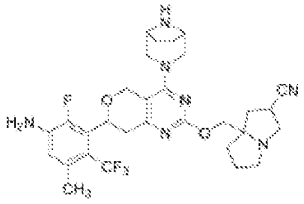
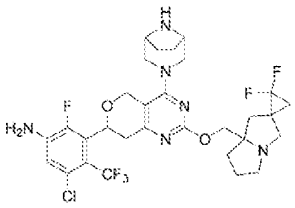
m is selected from 0, 1, 2, 3, 4, and 5;

provided that,

1) when Ring B is  substituted with one R_{10} and R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H;

2) when Ring B is  optionally substituted with 1, 2, 3, or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H; and

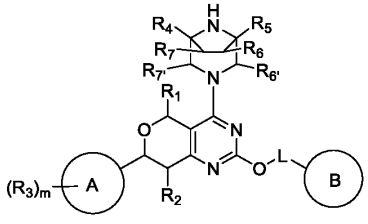
3) the compound is not

, , or .

In some embodiments, R_N is H.

In some embodiments, R_N is C_{1-3} alkyl optionally substituted with 1, 2, or 3 F or Cl.

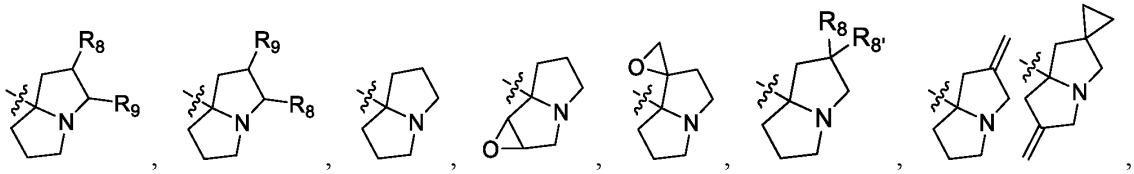
In some embodiments, the present disclosure provides a compound of Formula (I'):

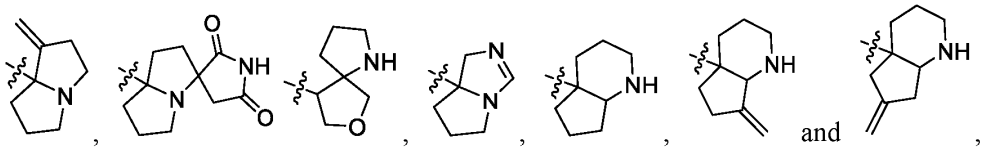

(I'),

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

Ring A is selected from the group consisting of C_6 aryl and 5-6 membered heteroaryl;

Ring B is selected from the group consisting of

,



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is $-CH_2-$ optionally substituted with 1 or 2 D;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN,C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3}alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, $-C(=O)-R_d$, $-C(=O)-NR_{b1}R_{b2}$, and $=NO(C_{1-3}$ alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and $-C(=O)-N(R_{b1})(R_{b2})$;

R_8 is selected from H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl; wherein the C_{3-5} cycloalkyl or 3-5 membered heterocyclyl is each independently optionally substituted with 1, 2 or 3 R_{10};

R_9 is $-C(=O)-NR_{b1}R_{b2}$ or $-CH_2R_c$;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3} alkylamino, $-S-R_d$, $-S(=O)-R_d$, $-S(=O)_2-R_d$, and $-NH-C(=O)-R_d$; wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH;

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, or 3 R_e;

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl;

R_c is selected from F, Cl, Br, I, OH, NH_2, $-O(C=O)NR_{C1}R_{C2}$, $-NR_{C0}(C=O)R_{C1}$, and $-NR_{C0}(C=O)NR_{C1}R_{C2}$;

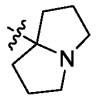
R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

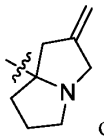
R_d is C_{1-3} alkyl;

R_e is selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkylamino, diC_{1-3} alkylamino, CN, C_{1-3} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl;

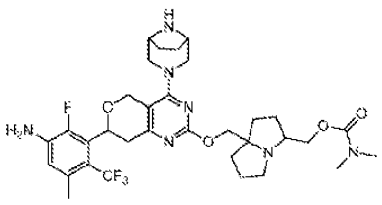
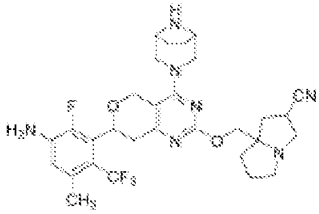
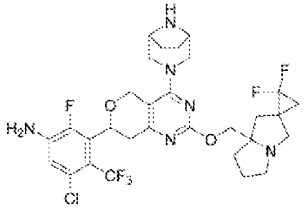
m is 0, 1, 2, 3, 4, or 5;

provided that,

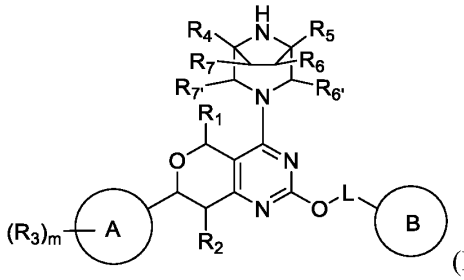
1) when Ring B is  optionally substituted with one R_{10} and when R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H;

2) when Ring B is  optionally substituted with 1, 2, 3, or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H; and

3) the compound is not

 ,  , or  .

In some embodiments, the present disclosure provides a compound of Formula (I'-1):

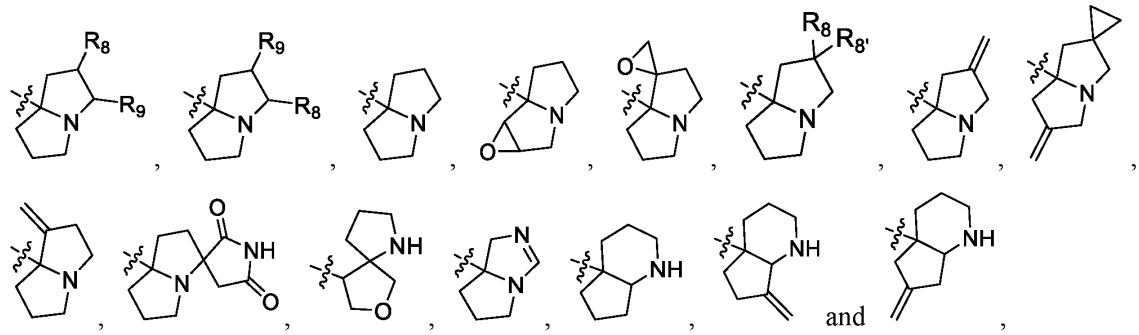


(I'-1),

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

Ring A is C_6 aryl;

Ring B is selected from



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is $-CH_2-$ optionally substituted with 1 or 2 D;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN,C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3}alkylamino, C_{2-4}alkenyl, C_{2-4} alkynyl and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, $-C(=O)-R_d$, $-C(=O)-NR_{b1}R_{b2}$, and $=NO(C_{1-3}$ alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and $-C(=O)-N(R_{b1})(R_{b2})$;

R_8 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl; wherein the C_{3-5} cycloalkyl and 3-5 membered heterocyclyl are each independently optionally substituted with 1, 2 or 3 R_{10};

R_9 is $-C(=O)-NR_{b1}R_{b2}$ or $-CH_2R_c$;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3} alkylamino, $-S-R_d$, $-S(=O)-R_d$, $-S(=O)_2-R_d$, and $-NH-C(=O)-R_d$; wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH;

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered

heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, or 3 R_e;

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl;

R_c is selected from F, Cl, Br, I, OH, NH_2, $-O(C=O)NR_{C1}R_{C2}$, $-NR_{C0}(C=O)R_{C1}$, and $-NR_{C0}(C=O)NR_{C1}R_{C2}$;

R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

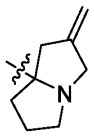
R_d is C_{1-3} alkyl;

R_e is selected from F, Cl, Br, I, OH, NH_2, C_{1-3} alkylamino, diC_{1-3} alkylamino, CN, C_{1-3} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl;

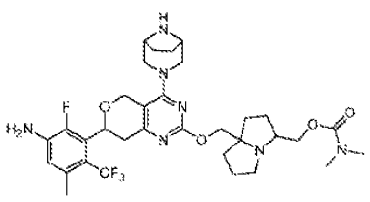
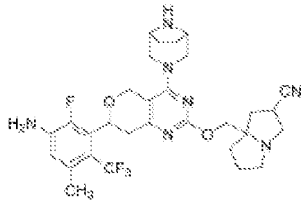
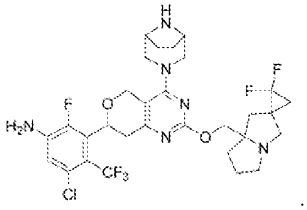
m is 0, 1, 2, 3, 4, or 5;

provided that,

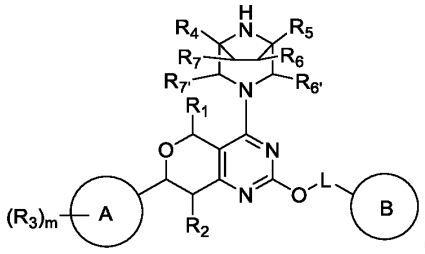
1) when Ring B is  optionally substituted with one R_{10} and when R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H;

2) when Ring B is  optionally substituted with 1, 2, 3 or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H; and

3) the compound is not

 ,  , or  .

In some embodiments, the present disclosure provides a compound of Formula (I'-2):

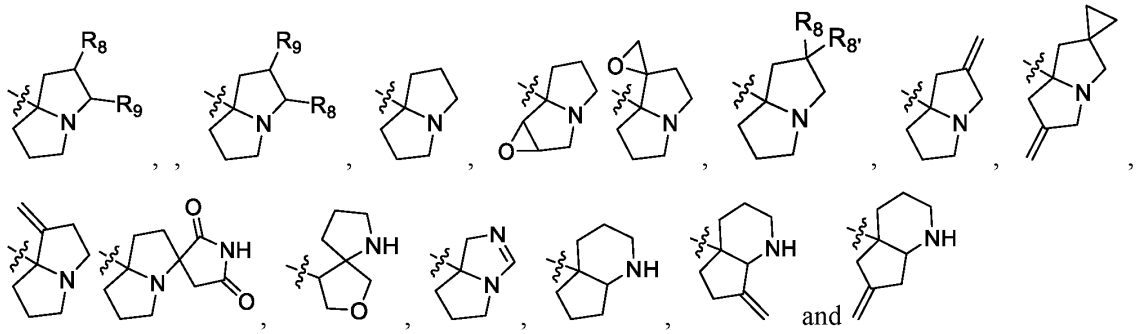


(I'-2),

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

Ring A is 5-membered heteroaryl;

Ring B is selected from



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is $-CH_2-$ optionally substituted with 1 or 2 D;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN,C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, diC_{1-3}alkylamino, C_{2-4}alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, $-C(=O)-R_d$, $-C(=O)-NR_{b1}R_{b2}$, and $=NO(C_{1-3}$ alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and $-C(=O)-N(R_{b1})(R_{b2})$;

R_8 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl; wherein the C_{3-5} cycloalkyl and 3-5 membered heterocyclyl are each independently optionally substituted with 1, 2 or 3 R_{10};

R_9 is selected from $-C(=O)-NR_{b1}R_{b2}$ and $-CH_2R_c$;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy,

C_{1-3} alkylamino, diC_{1-3} alkylamino, -S-R_d, -S(=O)-R_d, -S(=O)$_2$-R_d, and -NH-C(=O)-R_d; wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH;

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, or 3 R_e;

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl;

R_c is selected from F, Cl, Br, I, OH, NH_2, -O(C=O)N$R_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)N$R_{C1}R_{C2}$;

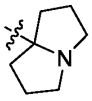
R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

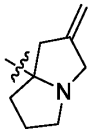
R_d is C_{1-3} alkyl;

R_e is selected from F, Cl, Br, I, OH, NH_2, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl;

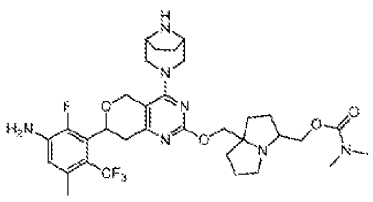
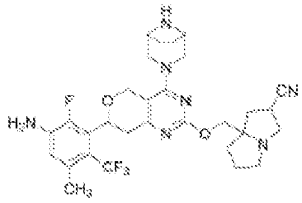
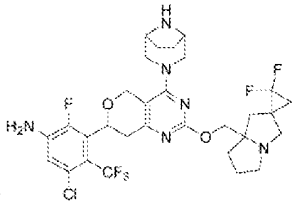
m is selected from 0, 1, 2, 3, 4 and 5;

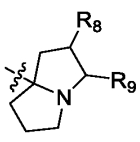
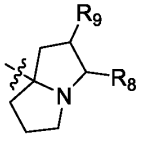
provided that,

1) when Ring B is  optionally substituted with one R_{10} and when R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H;

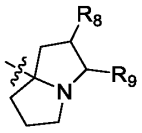
2) when Ring B is  optionally substituted with 1, 2, 3 or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H; and

3) the compound is not


, 
, or 
.

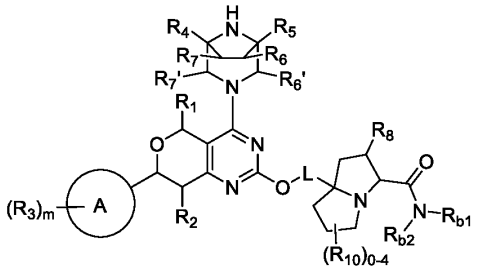
In some embodiments, Ring B is selected from  and , wherein Ring B

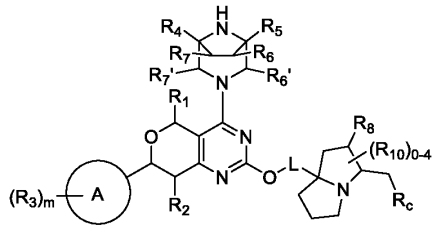
is optionally substituted with 1, 2, 3, or 4 R_{10}.

In some embodiments, ring B is  optionally substituted with 1, 2, 3, or 4 R_{10}. In some embodiments, Ring B is unsubstituted. In some embodiemnts, Ring B is substituted. In some embodiments, Ring B is substituted with 1 or 2 R_{10}. In some embodiments, Ring B is substituted with 1 R_{10}.

In any of the embodiments disclosed herein as applicable, Ring B is substituted with 2 R_{10}.

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, is a compound of Formula (I'-1-i), a compound of Formula (I'-2-i),

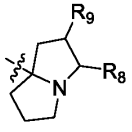

(I'-1-i),


(I'-2-i),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

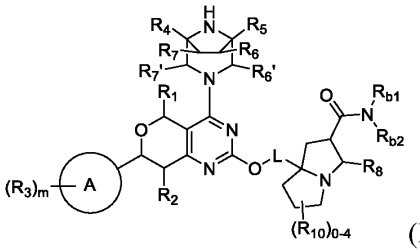
In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1-i), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof .

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-2-i), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

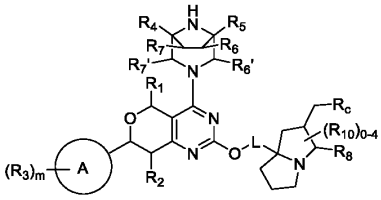
In some embodiments, Ring B is  optionally substituted with 1, 2, 3, or 4 R_{10}. In some embodiments, Ring B is unsubstituted. In some embodiments, Ring B is substituted with 1 or 2

R_{10}. In some embodiments, Ring B is substituted with 1 R_{10}. In some embodiments, Ring B is substituted with 2 R_{10}.

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1-ii), a compound of Formula (I'-2-ii),



(I'-1-ii),

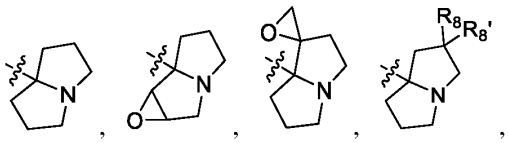
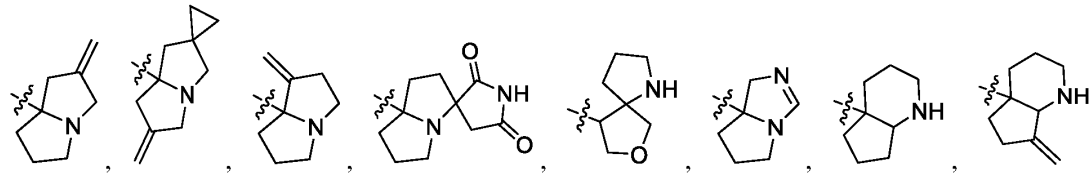
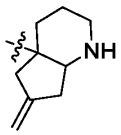


(I'-2-ii),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

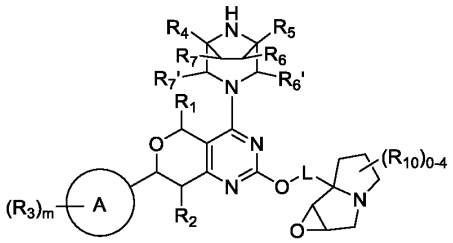
In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1-ii), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof .

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-2-ii), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

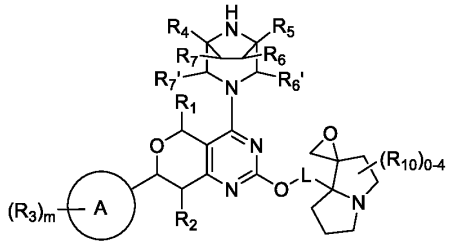
In some embodiments, Ring B is selected from , , and , wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10}. In some embodiments, Ring B is unsubstituted. In some embodiments, Ring B is substituted with 1 or 2 R_{10}. In some embodiments, Ring B is substituted with 1 R_{10}. In some embodiments, Ring B is substituted with 2

R_{10}.

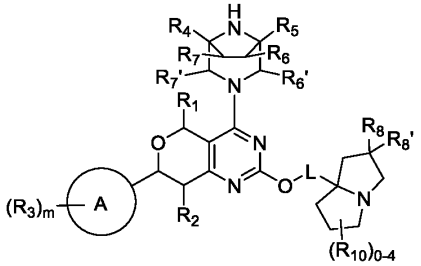
In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, is a compound of Formulae (I'-3), (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9), (I'-10), (I'-11), (I'-12), or (I'-13),



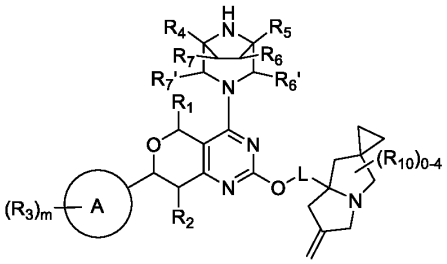
(I'-3),



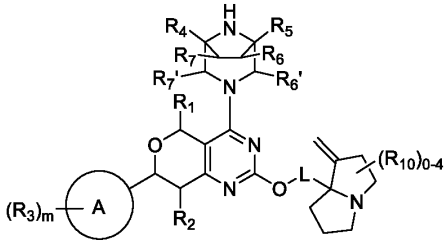
(I'-4),



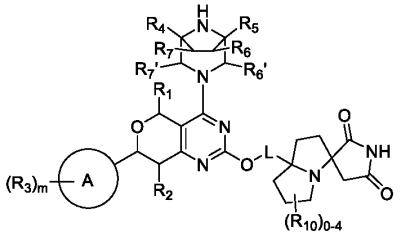
(I'-5),



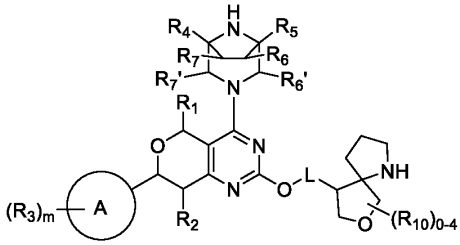
(I'-6),



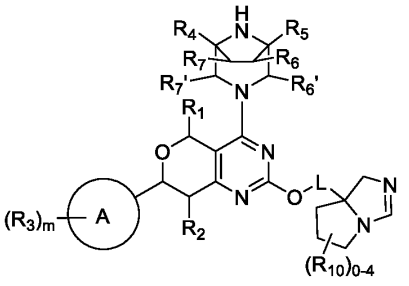
(I'-7),



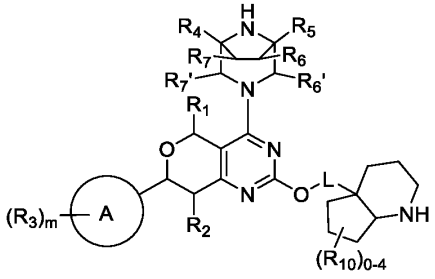
(I'-8),



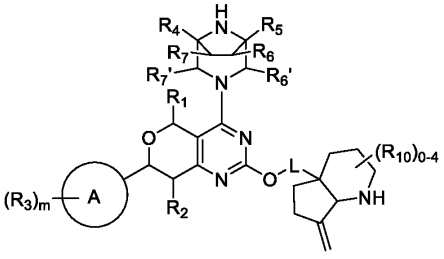
(I'-9),



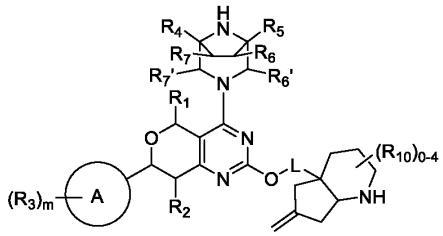
(I'-10),



(I'-11),



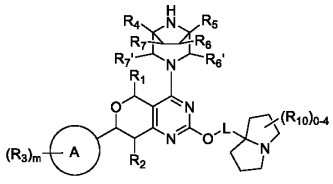
(I'-12),



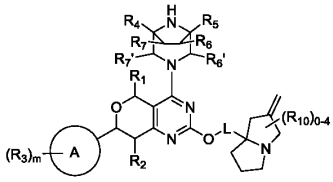
(I'-13),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, is a compound of Formula (I'-14), a compound of Formula (I'-15),



(I'-14),



(I'-15),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In any of the embodiments disclosed herein as applicable, Ring A is phenyl substituted with at least 1 R_3; wherein each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN , C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a.

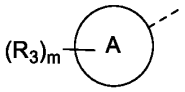
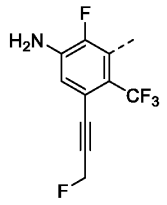
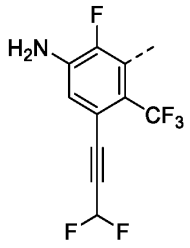
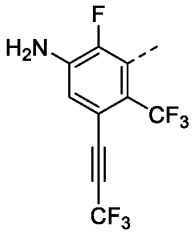
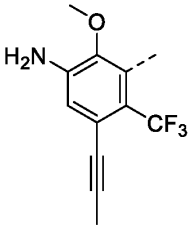
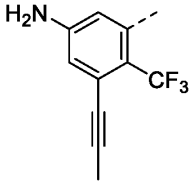
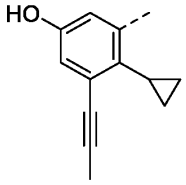
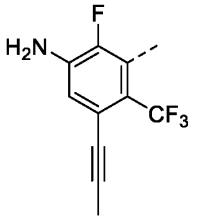
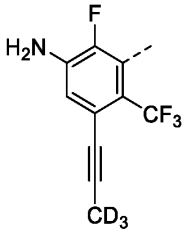
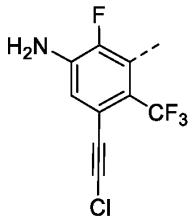
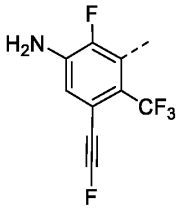
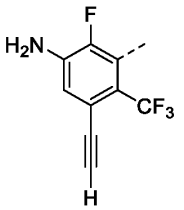
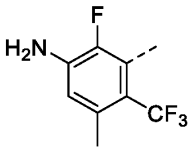
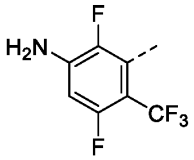
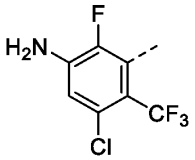
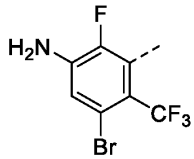
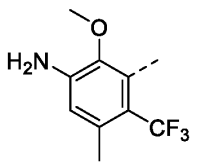
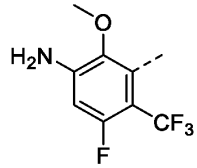
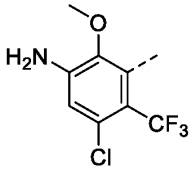
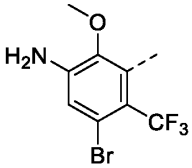
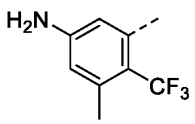
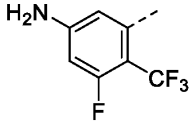
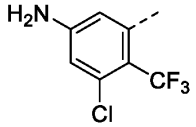
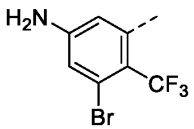
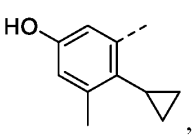
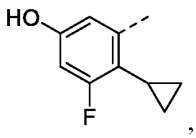
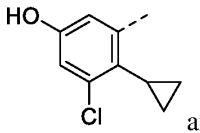
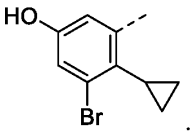
In any of the embodiments disclosed herein as applicable, Ring A is a 5-membered heteroaryl substituted with at least 1 R_3; wherein each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C{\equiv}CCH_3$, $-C{\equiv}CCH_2F$, $-C{\equiv}CCHF_2$, $-C{\equiv}CCF_3$, $-C{\equiv}CCD_3$, $-C{\equiv}CH$, $-C{\equiv}CCl$, $-C{\equiv}CF$ and cyclopropyl.

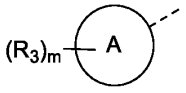
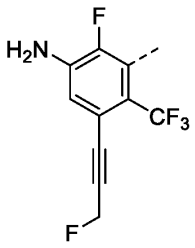
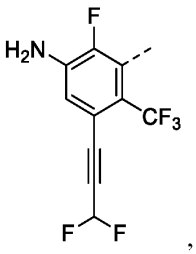
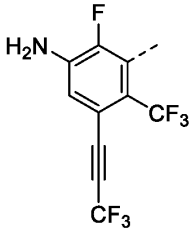
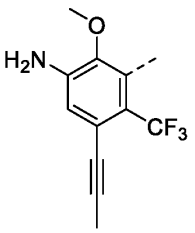
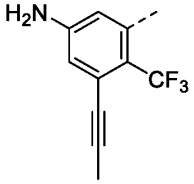
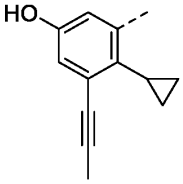
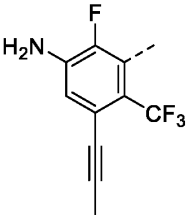
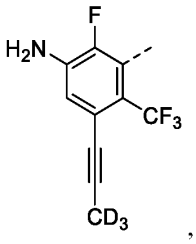
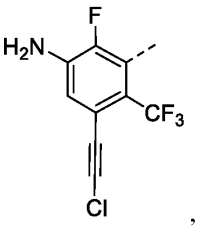
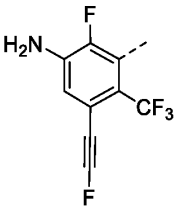
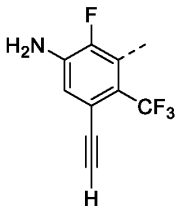
In some embodiments, Ring A is a 5-membered heteroaryl substituted with 2 R_3; wherein each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C{\equiv}CCH_3$, $-C{\equiv}CCH_2F$, $-C{\equiv}CCHF_2$, $-C{\equiv}CCF_3$, $-C{\equiv}CCD_3$, $-C{\equiv}CH$, $-C{\equiv}CCl$, $-C{\equiv}CF$ and cyclopropyl.

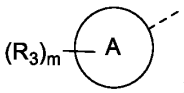
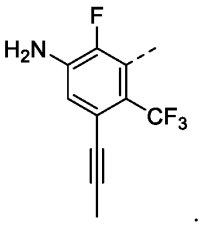
In any of the embodiments disclosed herein as applicable, Ring A is a 5-membered heteroaryl substituted with 3 R_3; wherein each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3,

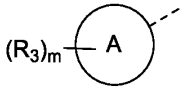
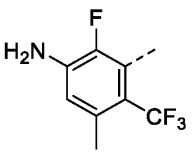
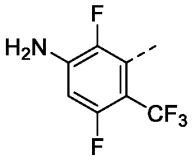
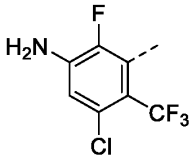
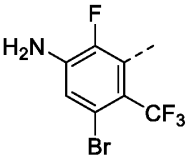
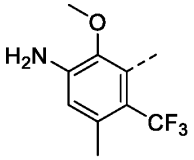
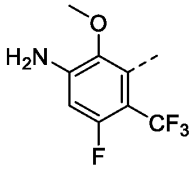
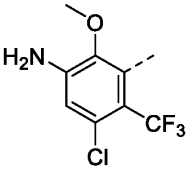
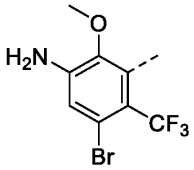
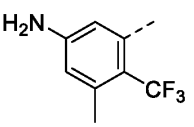
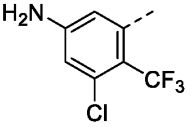
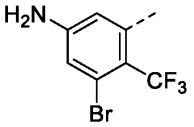
—C≡CCH$_3$, —C≡CCH$_2$F, —C≡CCHF$_2$, —C≡CCF$_3$, —C≡CCD$_3$, —C≡CH, —C≡CCl, —C≡CF and cyclopropyl.

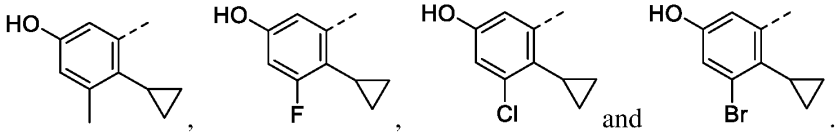
In any of the embodiments disclosed herein as applicable, Ring A is a 5-membered heteroaryl substituted with 4 R$_3$; wherein each R$_3$ is independently selected from F, OH, NH$_2$, CF$_3$, OCH$_3$, —C≡CCH$_3$, —C≡CCH$_2$F, —C≡CCHF$_2$, —C≡CCF$_3$, —C≡CCD$_3$, —C≡CH, —C≡CCl, —C≡CF and cyclopropyl.

In some embodiments,  is selected from , , , , , , , , , , , , , , , , , , , , , , , , , , .

In some embodiments,  is selected from , , , , , , , , , , and ,.

In any of the embodiments disclosed herein as applicable,  is .

In some embodiments,  is selected from , , , , , , , , , , , ,



and .

In any of the embodiments disclosed herein as applicable, Ring A is a 5-6 membered heteroaryl (e.g. pyridinyl) substituted with at least 1 R_3; each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN , C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 6 R_a.

In any of the embodiments disclosed herein as applicable, Ring A is a 5-6 membered heteroaryl (e.g., pyridyl) substituted with at least 1 R_3, each R_3 being independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, Ring A is a 5-6 membered heteroaryl (e.g., pyridyl) substituted with 2 R_3, each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 5-6 membered heteroaryl (e.g., pyridyl) substituted with 3 R_3, each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl. In some embodiments, ring A is selected from 5-6 membered heteroaryl (e.g., pyridyl) substituted with 4 R_3, each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 5-membered heteroaryl, substituted with at least 1 R_3; each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN , C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a.

In any of the embodiments disclosed herein as applicable, ring A is a 5-membered heteroaryl substituted with at least 1 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 5-membered heteroaryl substituted with at least 2 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 5-membered heteroaryl substituted with at least 3 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 5-membered heteroaryl substituted with at least 4 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 6-membered heteroaryl substituted with at least 1 R_3; each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN , C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl is independently substituted with 1, 2, 3, 4, or 6 R_a.

In any of the embodiments disclosed herein as applicable, ring A is a 6-membered heteroaryl substituted with at least 1 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

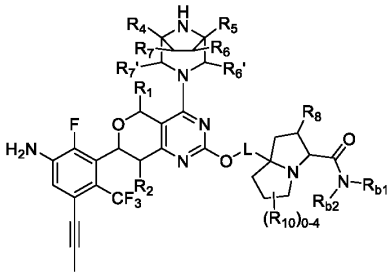
In any of the embodiments disclosed herein as applicable, ring A is a 6-membered heteroaryl substituted with at least 2 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In any of the embodiments disclosed herein as applicable, ring A is a 6-membered heteroaryl substituted with at least 3 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

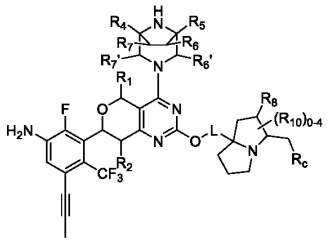
In any of the embodiments disclosed herein as applicable, ring A is a 6-membered heteroaryl substituted with at least 4 R_3; each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$,

—C≡CF and cyclopropyl.

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, is selected from a compound of Formula (I'-1'-i), a compound of Formula (I'-2'-i),



(I'-1'-i),



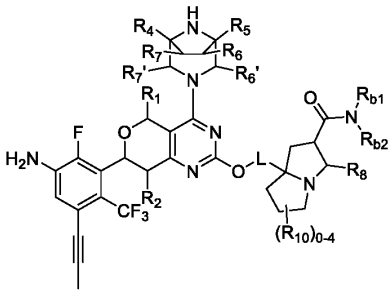
(I'-2'-i),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

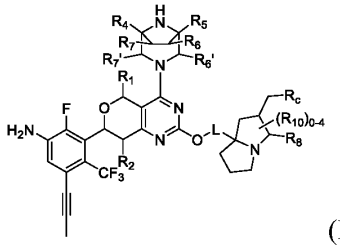
In any of the embodiments disclosed herein as applicable, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1'-i), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In any of the embodiments disclosed herein as applicable, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-2'-i), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1'-ii), a compound of Formula (I'-2'-ii),



(I'-1'-ii),



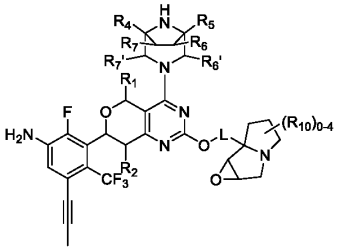
(I'-2'-ii),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

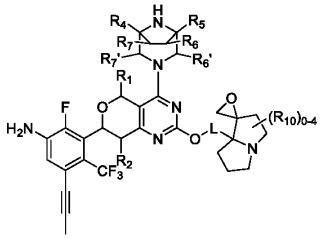
In any of the embodiments disclosed herein as applicable, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-1'-ii), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In any of the embodiments disclosed herein as applicable, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-2'-ii), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

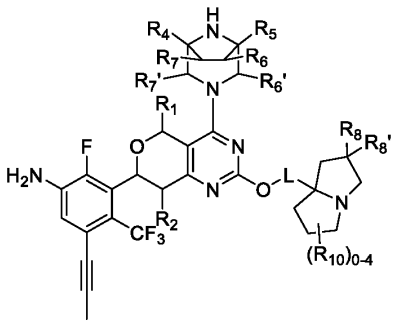
In some embodiments, the compound of Formula (I'-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is selected from a compound of Formulae (I'-3'), (I'-4'), (I'-5'), (I'-6'), (I'-7'), (I'-8'), (I'-9'), (I'-10'), (I'-11'), (I'-12'), (I'-13'),



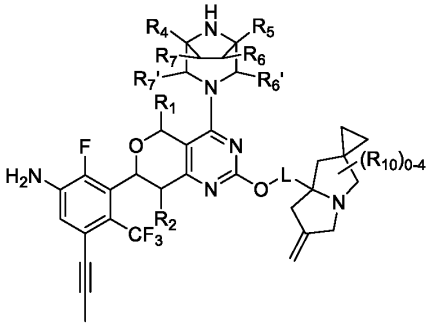
(I'-3'),



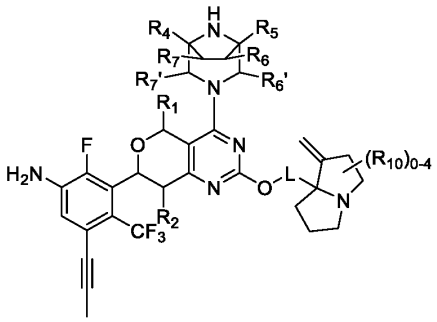
(I'-4'),



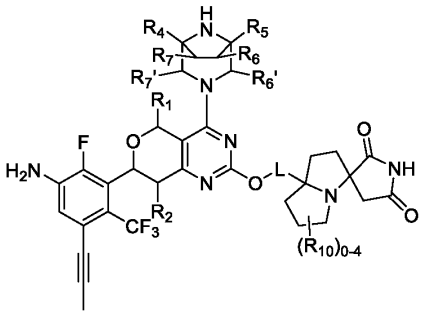
(I'-5'),



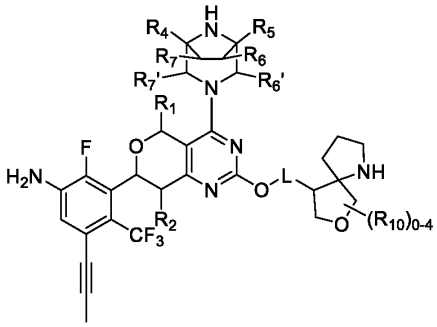
(I'-6'),



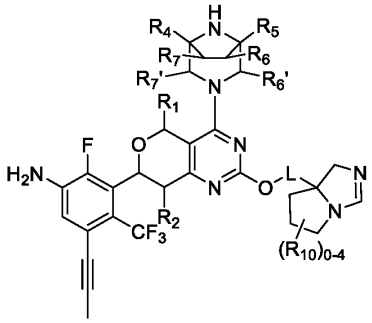
(I'-7'),



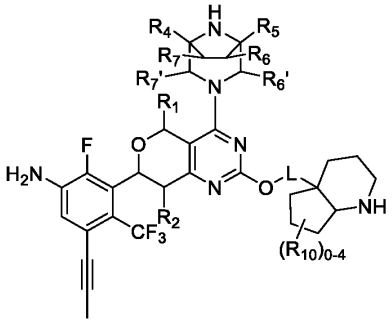
(I'-8'),



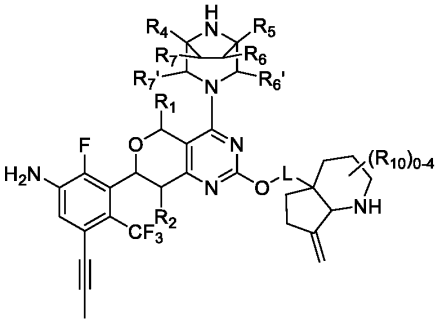
(I'-9'),



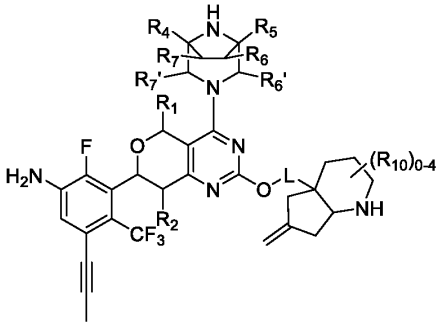
(I'-10'),



(I'-11'),



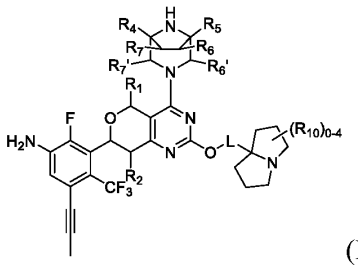
(I'-12'),



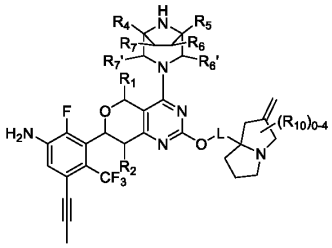
(I'-13'),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I'-1), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof is a compound of Formula (I'-14'), a compound of Formula (I'-15'),



(I'-14'),



(I'-15'),

a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, Ring A is selected from a C_6 aryl and a 5-6 membered heteroaryl (e.g., a ring containing 1-4 heteroatoms comprising O, N, or S).

In any of the embodiments disclosed herein as applicable, Ring A is phenyl. In any of the embodiments disclosed herein as applicable, Ring A is a 5-6 membered heteroaryl .

In any of the embodiments disclosed herein as applicable, Ring A is a 5-membered heteroaryl group.

In any of the embodiments disclosed herein as applicable, Ring A is a 6-membered heteroaryl group, as described herein.

In any of the embodiments disclosed herein as applicable, Ring A is unsubstituted.

In any of the embodiments disclosed herein as applicable, Ring A is substituted, as described herein.

In any of the embodiments disclosed herein as applicable, Ring A is substituted with at least 1 R_3 (e.g., 2, 3, or 4 R_3), as described herein.

In any of the embodiments disclosed herein as applicable, L is $-C(R_{L1}R_{L2})-$, and R_{L1} and R_{L2} are each independently selected from H and D.

In any of the embodiments disclosed herein as applicable, L is $-C(R_{L1}R_{L2})-$, and R_{L1} and R_{L2} are H.

In any of the embodiments disclosed herein as applicable, L is $-C(R_{L1}R_{L2})-$, and at least one of R_{L1} and R_{L2} is C_{1-3} alkyl.

In any of the embodiments disclosed herein as applicable, L is $-CH_2-$ optionally substituted with 1 or 2 D.

In any of the embodiments disclosed herein as applicable, L is $-CH_2-$.

In any of the embodiments disclosed herein as applicable, L is $-CD_2-$.

In any of the embodiments disclosed herein as applicable, L is -CHD-.

In some embodiments, L is selected from $-CH_2-$ and $-CD_2-$.

In some embodiments, R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN.

In any of the embodiments disclosed herein as applicable, R_1 and R_2 are H.

In some embodiments, R_1 is selected from oxo, H, F, Cl, Br, I, and CN.

In some schemes of the present invention, R_2 is selected from the oxo, F, Cl, and CN.

In some embodiments, R_2 is selected from oxo, H, F, Cl, Br, I, and CN.

In some embodiments, R_1 is selected from oxo, F, Cl, and CN.

In some embodiments, each R3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)), C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3)),, C_{1-3}-alkylamino (e.g., ethylamino, ethylamino, n-propylamino or isopropylamino), diC_{1-3}-alkylamino (e.g., dimethylamino, diethylamino, din-propyl) Amino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), C_{2-4} alkenyl (e.g., vinyl (C_2), 1-allyl(C_3), 2-allyl(C_3), 1-butenyl (C_4), 2-butenyl (C_4) or butadienyl (C_4)), C_{2-4} alkynyl (e.g. acetenyl (C_2), 1-propinyl(C_3), 2-propinyl(C_3), 1-butylenyl (C_4) or 2-butylenyl (C_4)) and C_{3-5} cycloalkyl（e.g., cyclopropyl(C_3), cyclobutyl(C_4), cyclopentyl(C_5)), wherein the C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylamino, diC_{1-3}alkylamino, C_{2-4}alkyl, C_{2-4} alkyl and C_{3-5} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a.

In some embodiments, each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C\equiv CCH_3$, $-C\equiv CCH_2F$, $-C\equiv CCHF_2$, $-C\equiv CCF_3$, $-C\equiv CCD_3$, $-C\equiv CH$, $-C\equiv CCl$, $-C\equiv CF$ and cyclopropyl.

In some embodiments, each R_a is independently selected from D, F, Cl, Br, and I.

In some embodiments, each R_a is independently selected from D, F, and I.

In some embodiments, m is selected from 0, 1, 2, 3, 4, and 5.

In any of the embodiments disclosed herein as applicable, m is 0.

In any of the embodiments disclosed herein as applicable, m is 1.

In any of the embodiments disclosed herein as applicable, m is 2.

In any of the embodiments disclosed herein as applicable, m is 3.

In any of the embodiments disclosed herein as applicable, m is 4.

In any of the embodiments disclosed herein as applicable, m is 5.

In some embodiments, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH2, CN, and C_{1-3} alkyl (such as methyl (C_1), ethyl (C_2), n-propyl (C_3), or isopropyl (C_3)), C_2-4 alkenyl (such as vinyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), or butadienyl (C_4)), C_{1-3} alkoxy (such as methoxy (C_1), ethoxy (C_2), propoxy (C_3), or isopropoxy (C_3)), -C(=O)-Rd, -C(=O)-NRb1Rb2, and =NO(C_{1-3} alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted by 1, 2, 3, 4, or 5 Rb.

In any of the embodiments disclosed herein as applicable, R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ independently are H.

In any of the embodiments disclosed herein as applicable, at least one of R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ is not H.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-membered heterocyclyl, comprising 1 heteroatom selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-membered heterocyclyl, wherein the heterocyclyl comprises 1 heteroatom selected from N and O.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 4-membered heterocyclyl, wherein the heterocyclyl comprises 1 heteroatom selected from N, O and S.

In any of the embodiments disclosed herein as applicable R_6 and R_7 together with the carbon atoms to which they are attached form a 4-membered heterocyclyl, wherein the heterocyclyl comprises 1-2 heteroatoms selected from N and O. In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 4-membered heterocyclyl, wherein the heterocyclyl comprises 1 heteroatom selected from N and O.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 5-membered heterocyclyl, wherein the heterocyclyl comprises 1-2 heteroatoms selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_6 and R_7 together with the carbon atoms to which they are attached form a 5-membered heterocyclyl, wherein the heterocyclyl comprises 1-2 heteroatoms selected from N andO.

In any of the embodiments disclosed herein as applicable, R_6 and $R_{7'}$ together with the carbon

atoms to which they are attached form a 5-membered heterocyclyl, wherein the heterocyclyl comprises 1-2 heteroatoms selected from N and O.

In some embodiments, each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropoxy(C_3)), and -C(=O)-$NR_{b1}R_{b2}$.

In some embodiments, each R_b is independently selected from D, F, Cl, OH, NH_2, CN, C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropoxy(C_3)), and -C(=O)-$NR_{b1}R_{b2}$.

In some embodiments, R_8 is selected from H, F, Cl, Br, I, OH, NH2, CN, C_{1-3} alkyl (such as methyl (C_1), ethyl (C_2), n-propyl (C_3), or isopropyl (C_3)), and C_{1-3} alkoxy (such as methoxy (C_1), ethoxy (C_2), propoxy (C_3), or isopropoxy (C_3)), wherein the C_{1-3} alkyl and C_{1-3} alkoxy groups independently are optionally substituted with 1, 2, 3, 4, or 5 R_a.

In any of the embodiments disclosed herein as applicable, R_8 is H.

In any of the embodiments disclosed herein as applicable, R_8 is selected from F, Cl, Br, I, OH, NH2, CN, C_{1-3} alkyl (such as methyl (C_1), ethyl (C_2), n-propyl (C_3), or isopropyl (C_3)), and C_{1-3} alkoxy (such as methoxy (C_1), ethoxy (C_2), propoxy (C_3), or isopropoxy (C_3)), wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5a.

In any of the embodiments disclosed herein as applicable, R_8 is selected from F, Cl, Br, I, OH, NH2, N, C_{1-3} alkyl (such as methyl (C_1), ethyl (C_2), n-propyl (C_3), or isopropyl (C_3)), and C_{1-3} alkoxy (such as methoxy (C_1), ethoxy (C_2), propoxy (C_3), or isopropoxy (C_3)), wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5a.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a C_{3-5} cycloalkyl (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5)) or 3-5 membered heterocyclyl (e.g., heterocyclyl includes a ring comprising 1-3 heteroatoms selected from O, N and S), wherein the C_{3-5} cycloalkyl or 3-5 membered heterocyclyl is independently optionally substituted with 1, 2 or 3 R_{10}.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a C_{3-5} cycloalkyl group (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5wherein the cycloalkyl group is optionally substituted with 1, 2, or 3 R_{10}.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl (e.g., a 3-5 heterocyclyl includes a ring comprising 1 to 2 heteroatoms selected from O, N, and S), wherein the 3-5 membered heterocyclyl is independently optionally substituted with 1, 2, or 3 R_{10}.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 3-membered heterocyclyl, wherein theheterocyclyl comprises 1 heteroatom selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 3-membered heterocyclyl comprising 1 heteroatom selected from N and O.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 4-membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 4-membered heterocyclyl group comprising 1-2 heteroatoms selected from N and O.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 4-membered heterocyclyl comprising one heteroatom selected from N and O.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 5-heterocyclyl comprising 1-2 heteroatoms selected from N, O and S.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 5-heterocyclyl group comprising 1-2 heteroatoms selected from N and O.

In any of the embodiments disclosed herein as applicable, R_8 and $R_{8'}$ together with the carbon atoms to which they are attached form a 5-membered heterocyclyl comprising one heteroatom selected from N and O.

In any of the embodiments disclosed herein as applicable, R_9 is selected from $-C(=O)-NR_{b3}R_{b4}$ and $-CH_2R_c$.

In any of the embodiments disclosed herein as R_9 is $-C(=O)-NR_{b3}R_{b4}$.

In any of the embodiments disclosed herein as applicable, R_9 is $-CH_2R_c$.

In any of the embodiments disclosed herein as applicable, R_9 is $-C(=O)-NR_{b1}R_{b2}$.

In some embodiments, each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)), C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3)), C_{1-3} alkylamino (e.g., methylamino, ethylamino, n-propylamino, or isopropylamino)), diC_{1-3} alkylamino (e.g., dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), $-C(=O)-R_d$, $-S-R_d$, $-S(=O)-R_d$, $-S(=O)_2-R_d$, $-NH-C(=O)-R_d$, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F, and the C_{6-10} aryl and 5-10

membered heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}.

In some embodiments, at least one R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)), C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3)), C_{1-3} alkylamino (e.g., methylamino, ethylamino, n-propylamino, or isopropylamino)), diC_{1-3} alkylamino (e.g., dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), -S-R_d, -S(=O)-R_d, -S(=O)$_2$-R_d and -NH-C(=O)-R_d, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F.

In some embodiments, at least one R_{10} is independently selected from oxo, D, F, Cl, OH, NH_2, CN, C_{1-3} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)), C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3)), C_{1-3} alkylamino (e.g., methylamino, ethylamino, n-propylamino, or isopropylamino)), diC_{1-3} alkylamino (e.g., dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), -S-R_d, -S(=O)-R_d, -S(=O)$_2$-R_d and -NH-C(=O)-R_d, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F.

In some embodiments, at least one R_{10} is independently selected from oxo, F, Cl, C_{1-3} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)), C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3)), C_{1-3} alkylamino (e.g., methylamino, ethylamino, n-propylamino, or isopropylamino)), diC_{1-3} alkylamino (e.g., dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), wherein theC_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F.

In some embodiments, at least one R_{10} is selected from -C(=O)-R_d, -S-R_d , -S(=O)-R_d , -S(=O)$_2$-R_d and -NH-C(=O)-R_d.

In some schemes of the present invention, at least one R_{10} is selected from C_{6-10} aryl and 5-10 membered heteroaryl, wherein the C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} have at least one group selected from C_{1-6} alkyl (e.g., methyl (C_1), ethyl (C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), isobutyl (C_4), m-butyl (C_4), tert-butyl (C_4), pentyl (C_5) or hexyl (C_6)), C_{1-6} alkoxy (e.g, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), C_{3-10}cycloalkyl (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl

(C_5), cyclohexyl (C_6), cycloheptyl (C_7), cyclooctyl (C_8), bicyclic [2.2.1] heptyl (C_7), bicyclic [2.2.2] octyl (C_8), cyclononyl (C_9), cyclodecyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthyl (C_{10}) or spiro[4.5]decyl (C_{10})), 3-10 heterocyclyl (e.g., heterocyclyl includes one or two 3-8 membered rings comprising1-5 heteroatoms selected from N, O and S), C_{6-10} aryl (e.g., phenyl or naphthyl) and 5-10 membered heteroaryl (e.g., heteroaryl comprises one or two 5-membered or 6-membered rings comprising 1-5 heteroatoms selected from N, O and S), wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3 or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} have at least one group selected from C_{1-6} alkyl (e.g., methyl (C_1), Ethyl (C_2), N-propyl (C_3), Isopropyl (C_3), n-butyl (C_4), Isobutyl (C_4), m-butyl (C_4), tert-butyl (C_4), pentyl (C_5) or hexyl (C_6)), C_{1-6} alkoxy (e.g, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), C_{3-10}cycloalkyl (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6), ring heptyl (C_7), cyclooctyl (C_8), Double ring[2.2.1]Heptyl (C_7), Double ring[2.2.2]octyl (C_8), Cyclinyl (C_9), ring decyl (C_10), octahydro-1H-indenyl (C_9), decahydronaphthyl (C_{10}) or spiro[4.5]decyl (C_{10})), 3-10 membered heterocyclyl (e.g., heterocyclyl includes one or two 3-8 membered rings comprising 1-5 heteroatoms selected from N, oO and S, wherein the heterocyclyl may be monocyclic or polycyclic, such as spiro rings, bridging rings or fused polycyclic rings), C_{6-10} aryl (e.g., phenyl or naphthyl) and 5-10 membered heteroaryl (e.g., heteroaryl comprises one or two 5-membered or 6-membered rings comprising 1-5 heteroatoms selected from N, O and S), wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3 or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} have at least one group selected from C_{1-6} alkyl (e.g., methyl (C_1), ethyl (C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), isobutyl (C_4), m-butyl (C_4), tert-butyl (C_4), pentyl (C_5) or hexyl (C_6)), and C_{1-6} alkoxy (e.g, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), wherein the C_{1-6} alkyl and C_{1-6} alkoxy are each independently optionally substituted with 1, 2, 3 or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} have at least one group selected from C_{3-10}cycloalkyl (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6), cycloheptyl (C_7), cyclooctyl (C_8), bicyclic [2.2.1] heptyl (C_7), bicyclic [2.2.2] octyl (C_8), cyclononyl (C_9), cyclodecyl (C_10), octahydro-1H-indenyl (C_9), decahydronaphthyl (C_{10}) or spiro[4.5]decyl (C_{10})), 3-10 heterocyclyl (e.g., heterocyclyl includes one or two 3-8 membered rings comprising 1-5 heteroatoms selected from N, O and S), C_{6-10} aryl (e.g., phenyl or naphthyl) and 5-10

membered heteroaryl (e.g., heteroaryl comprises one or two 5-membered or 6-membered rings comprising 1-5 heteroatoms selected from N, O and S), wherein the C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3 or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} have at least one group selected from C_{3-6}cycloalkyl (e.g., cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), Cyclohexyl (C_6)), 3-6 heterocyclyl, C_6 aryl and 5-6 membered heteroaryl (e.g., heteroaryl comprises 1-3 heteroatoms selected from N, O and S), wherein theC_{3-6} cycloalkyl, 3-6 membered heterocyclyl, C_6 aryl and 5-6 membered heteroaryl are each independently optionally substituted with 1, 2, 3 or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b1} and R_{b2} together with the nitrogen atoms to which they are attached form a 3-6 membered heterocyclyl (e.g., heterocyclyl comprises 1-4 heteroatoms selected from N, O and S) , wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{e1}.

In any of the embodiments disclosed herein as applicable, R_{b3} and R_{b4} are each independently H, C_{1-6} alkyl, C_{1-6} alkoxy (e.g, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings comprising 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1, 2, 3, or 4 R_{e2}.

In any of the embodiments disclosed herein as applicable, at least one of R_{b1} and R_{b2} is C_{1-6} alkyl or C_{1-6} alkoxy (e.g, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), wherein the alkyl or alkoxy is optionally substituted with 1, 2, 3, or 4 R_{e2}.

In any of the embodiments disclosed herein as applicable, at least one of R_{b1} and R_{b2} is C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8),

cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1, 2, 3, or 4 R_{e2}.

In any of the embodiments disclosed herein as applicable, at least one of R_{b1} and R_{b2} is C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6)), 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising 1-3 heteroatoms selected from N, O, and S), C_6 aryl, 5- to 6-membered heteroaryl (*e.g.*, heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1, 2, 3, or 4 R_{e2}.

In any of the embodiments disclosed herein as applicable, R_{b3} and R_{b4}, together with nitrogen atom to which they are attached, form 3-6 membered heterocyclyl (*e.g.*, heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S), wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{e2}.

In any of the embodiments disclosed herein as applicable, R_c is selected from F, Cl, Br, I, OH, NH_2, -(C=O)$NR_{C1}R_{C2}$, -O(C=O)$NR_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)$NR_{C1}R_{C2}$. In some embodiments, R_c is selected from the group consisting of F, Cl, OH, NH_2, -O(C=O)$NR_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)$NR_{C1}R_{C2}$. In some embodiments, R_c is selected from F, Cl, -O(C=O)$NR_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)$NR_{C1}R_{C2}$. In some embodiments, R_c is selected from the group consisting of F, Cl, OH, and NH_2. In some embodiments, R_c is selected from -O(C=O)$NR_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)$NR_{C1}R_{C2}$.

In any of the embodiments disclosed herein as applicable, R_{C0}, R_{C1} and R_{C2} are each independently selected from H, C_{1-6} alkyl (e.g., methyl(C_1), ethyl(C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), isobutyl (C_4), metabutyl (C_4), tert-butyl (C_4), pentyl (C_5) or hexyl (C_6)), C_{3-6} cycloalkyl (e.g., cyclopropyl(C_3), cyclobutyl (C_4), cyclopentyl(C_5), cyclohexyl (C_6)) and 3-6 membered heterocyclyl (e.g., heterocyclyl includes one or two 3-6 membered rings comprising 1-4 heteroatoms selected from N, O and S).

In any of the embodiments disclosed herein as applicable, R_d is selected from C_{1-3} alkyl (e.g.,

methyl(C_1), ethyl(C_2), n-propyl(C_3) or isopropyl(C_3)).

In any of the embodiments disclosed herein as applicable, R_{e1} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), -$S(=O)_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), -(C=O)N(C_{1-3} alkyl)$_2$, C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S).

In any of the embodiments disclosed herein as applicable, R_{e1} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), -$S(=O)_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{e1} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, or C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)). In certain embodiments, R_{e1} is -$S(=O)_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{e1} is selected from F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (e.g., methylamino, ethylamino, n-propylamino or isopropylamino), diC_{1-3} alkylamino (e.g., dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl ethylamine, methyl n-propylamino, methyl isopropylamino, ethyl n-propyl amino, ethyl isopropylamino or n-propyl isopropylamino), CN, C_{1-3} alkoxy (e.g., methoxy(C_1), ethoxy(C_2), propoxy(C_3) or isopropyloxy(C_3), C_{3-10} cycloalkyl (e.g., cyclopropyl(C_3), cyclobutyl(C_4), cyclopentyl(C_5), cyclohexyl (C_6), cycloheptyl (C_7), cyclooctyl (C_8), bicyclic [2.2.1] heptyl (C_7), bicyclic [2.2.2] octyl (C_8), cyclononyl (C_9), cyclodecyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthyl (C_{10}), or spiro[4.5]decyl (C_{10})), 3-10 membered heterocyclyl, (e.g., heterocyclyl includes one or two 3-8 membered rings comprising 1-5 heteroatoms selected from N, O and S, wherein heterocyclyl may be monocyclic or polycyclic, such as spiro rings, bridging rings or fused polycyclic rings), C_{6-10} aryl (e.g., phenyl or naphthyl) and 5-10 membered heteroaryl (e.g., heteroaryl comprises one or two 5-membered or 6-membered rings and 1-5 rings selected from heteroatoms N, O and S).

In any of the embodiments disclosed herein as applicable, R_{e1} is C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S).

In any of the embodiments disclosed herein as applicable, R_{e2} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), -(C=O)N(C_{1-3} alkyl)$_2$, C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6),

cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the cycloalkyl, heterocyclyl, aryl, and heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}, and wherein the alkyl and alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2}.

In any of the embodiments disclosed herein as applicable, R_{e2} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), -$S(=O)_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$, wherein the alkyl and alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2}.

In any of the embodiments disclosed herein as applicable, R_{e2} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, or C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), wherein the alkyl and alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2}.

In any of the embodiments disclosed herein as applicable, R_{e2} is -$S(=O)_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{e2} is F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), or *i*-propyl (C_3)), C_{1-3} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-3} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-

propylamino), CN, C_{1-3} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), or *i*-propoxy (C_3)), C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the cycloalkyl, heterocyclyl, aryl, and heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}, and wherein the alkyl and alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2}.

In any of the embodiments disclosed herein as applicable, R_{e2} is C_{3-10} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 10-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S, wherein the heterocyclyl can be monocyclic or polycyclic such as spiro, bridged, or fused polycyclic ring), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S) , wherein the cycloalkyl, heterocyclyl, aryl, and heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}.

In any of the embodiments disclosed herein as applicable, two R_{e2} together with the carbon atoms to which they are attached form a C_6 aryl or 5- or 6-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S).

In any of the embodiments disclosed herein as applicable, R_{s1} is oxo, F, Cl, Br, I, OH, NH_2, NO_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino,

ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s1} is oxo, F, Cl, Br, I, OH, NH_2, NO_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, or C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)).

In any of the embodiments disclosed herein as applicable, R_{s1} is C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s1} is oxo, F, Cl, Br, I, OH, NH_2, NO_2, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s1} is -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s2} is F, Cl, Br, I, OH, NH_2, C_{1-6} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s2} is F, Cl, Br, I, OH, NH_2, C_{1-6}

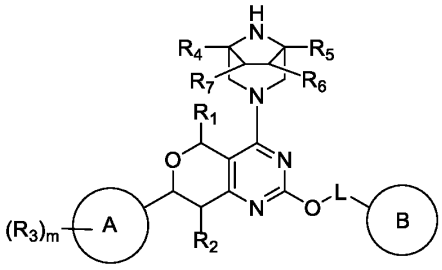
alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, or C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)).

In any of the embodiments disclosed herein as applicable, R_{s2} is C_{1-6} alkylamino (*e.g.*, methylamino, ethylamino, *n*-propylamino, or *i*-propylamino), di-C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, or *n*-propyl-*i*-propylamino), CN, C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), hexyloxy (C_6)), -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s2} is F, Cl, Br, I, OH, NH_2, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

In any of the embodiments disclosed herein as applicable, R_{s2} is -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), or -(C=O)N(C_{1-3} alkyl)$_2$.

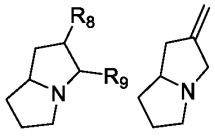
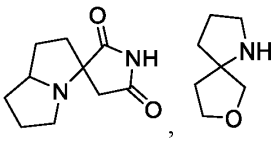
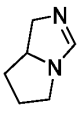
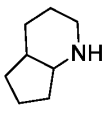
In certain aspects, the present disclosure provides a compound of Formula (I):

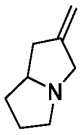
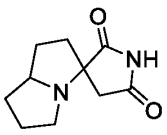
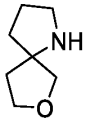
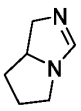
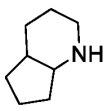


(I) ,

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

Ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl;

Ring B is selected from  ,  ,  and  ,

wherein  ,  ,  ,  , and  are each independently

optionally substituted with 1, 2, 3, or 4 R_{10};

L is -CH_2-, wherein the -CH_2- is optionally substituted with 1 or 2 D;

R_1 and R_2 are each independently selected from H, F, Cl, Br, I, C_{1-3} alkyl, and C_{3-5} cycloalkyl; wherein the C_{1-3} alkyl and C_{3-5} cycloalkyl are each independently optionally substituted with 1, 2, or 3 R_a;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl; wherein the C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3} alkylamino, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{3-5} cycloalkyl are each independently substituted with 1, 2, 3, 4, or 5 R_a;

R_4, R_5, R_6 and R_7 is selected from the group consisting of H, OH, NH_2, CN, C_{1-3}alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

R_8 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

R_9 is selected from -C(=O)-$NR_{b1}R_{b2}$ and -CH_2R_c;

each R_{10} is independently selected from D, F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkylamino, and -NH-C(=O)-R_d;

each R_a is independently selected from D, F, Cl, Br, and I;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, and -C(=O)-$NR_{b1}R_{b2}$;

R_{b1} and R_{b2} are each independently selected from H and C_{1-3} alkyl;

R_c is selected from F, Cl, Br, I, OH, and NH_2;

R_d is C_{1-3} alkyl;

m is selected from 0, 1, 2, 3, 4 and 5.

In some embodiments, the abovementioned L is selected from the group consisting of -CH_2- and -CD_2-, and other variables are as defined in the present invention.

In some embodiments, R_a is independently selected from the group consisting of D, F, and Cl, with other variables as defined in the present invention.

In some embodiments, R_b is independently selected from OH, CN, and -C(=O)-NH_2, and other variables are as defined in the present invention.

In some embodiments, R_{b1} and R_{b2} are each independently selected from H and CH_3, and other variables are as defined in the present invention.

In some embodiments, R_c is OH.

In some embodiments of the present disclosure, the R_d is CH_3, while other variables are as defined

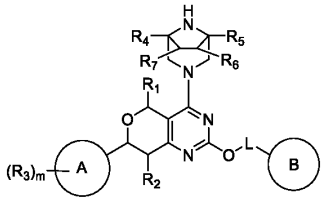
herein.

In some embodiments, R_1 is H.

In some embodiments, R_2 is H.

In some embodiments, R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, CH_3, CH_2CH_3, OCH_3, O CH_2CH_3, $NHCH_3$, $N(CH_3)_2$, —C≡CH, —C≡CCH$_3$, cyclopropyl and cyclobutyl, wherein the CH_3, CH_2CH_3, O CH_3, O CH_2CH_3, $NHCH_3$, $N(CH_3)_2$, —C≡CH, —C≡CCH$_3$, cyclopropyl and cyclobutyl are each independently optionally substituted with 1, 2, 3, 4 or 5 R_a.

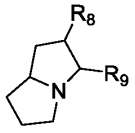
In some embodiments, the present invention provides a compound of formula (I-a)



(I-a) ,

or a pharmaceutically acceptable salt thereof wherein:

Ring A is selected from the group consisting of C_6 aryl and 5-membered heteroaryl;

Ring B is  ;

wherein variables in formula (I-a) are as defined in formula (I).

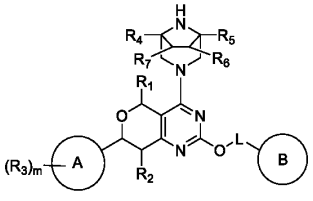
In some embodiments, the compound of formula (I), or a pharmaceutically acceptable salt thereof, is the compound of formula (I-a), or a pharmaceutically acceptable salt thereofm wherein: or the pharmaceutically acceptable salt thereof, in

Ring A is C_6 aryl.

In some embodiments, the compound of formula (I-a), is apharmaceutically acceptable salt thereof, wherein:

ring A is 5-membered heteroaryl.

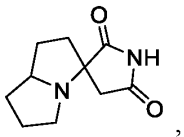
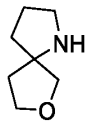
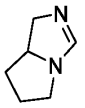
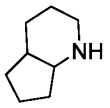
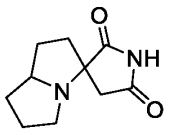
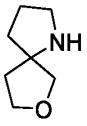
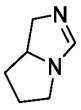
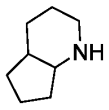
In certain aspects, the present disclosureprovides a compound of formula (I-b),



(I-b) ,

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from C_6 aryl and 5-membered heteroaryl;

Ring B is selected from , ,  and , wherein the , , , and  are each independently optionally substituted with 1, 2, 3, or 4 R_{10};

wherein variables in formula (I-b) are as defined in formula (I).

In some embodiments, the compound of formula (I-b) above, or the pharmaceutically acceptable salt thereof, Ring A is C_6 aryl.

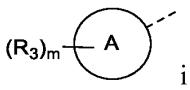
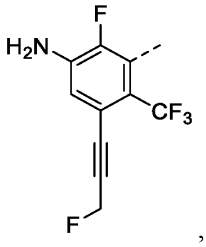
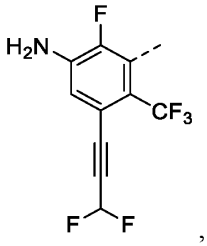
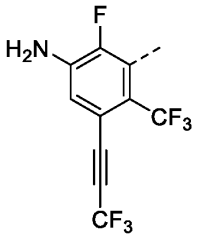
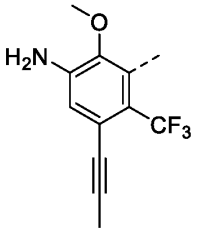
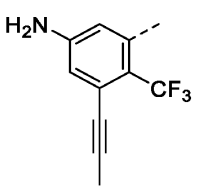
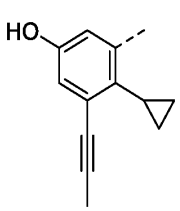
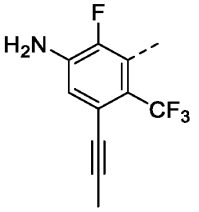
In some embodiments, the compound of formula (I-b) , is a pharmaceutically acceptable salt thereof,

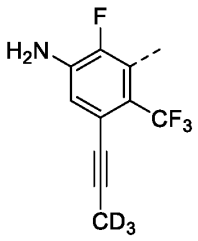
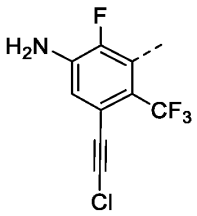
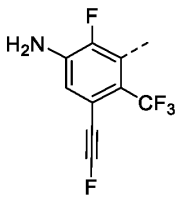
wherein ring A 5-membered heteroaryl.

In some embodiments, R_3 is independently selected from F, OH, NH_2, CF_3, O CH_3, $-C{\equiv}CCH_3$, $-C{\equiv}CCH_2F$, $-C{\equiv}CCHF_2$, $-C{\equiv}CCF_3$, $-C{\equiv}CCD_3$, $-C{\equiv}CCl$, $-C{\equiv}CF$ and cyclopropyl.

wherein other variables as defined in the present invention.

In some embodiments, ring A is phenyl.

In some embodiments,  is selected from , , , , , , ,



and .

In some embodiments, R_5 is selected from H, OH, NH_2, CN, CH_3, CH_2CH_3, OCH_3, and O CH_2CH_3, wherein the H, OH, NH_2, CN, CH_3, CH_2CH_3, OCH_3, and O CH_2CH_3 are each independently optionally substituted with 1, 2, 3, 4, or 5_b, as valency permits.

In some embodiments, R_5 is selected from H, CH_3, CH_2CN, CH_2OH and CH_2CONH_2.

In some embodiments, R_6 is selected from H and OH.

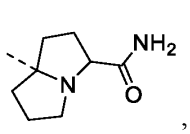
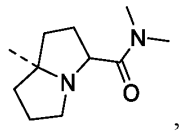
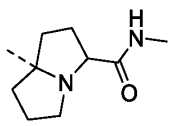
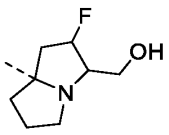
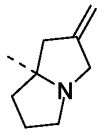
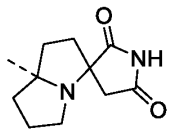
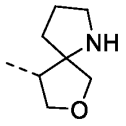
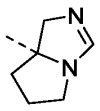
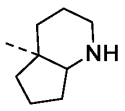
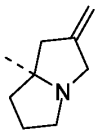
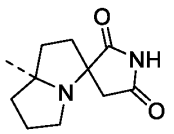
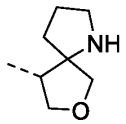
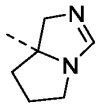
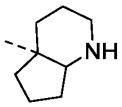
In some embodiments, R_4 is H.

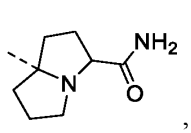
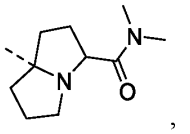
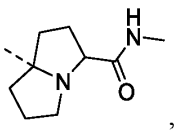
In some embodiments, R_7 is H.

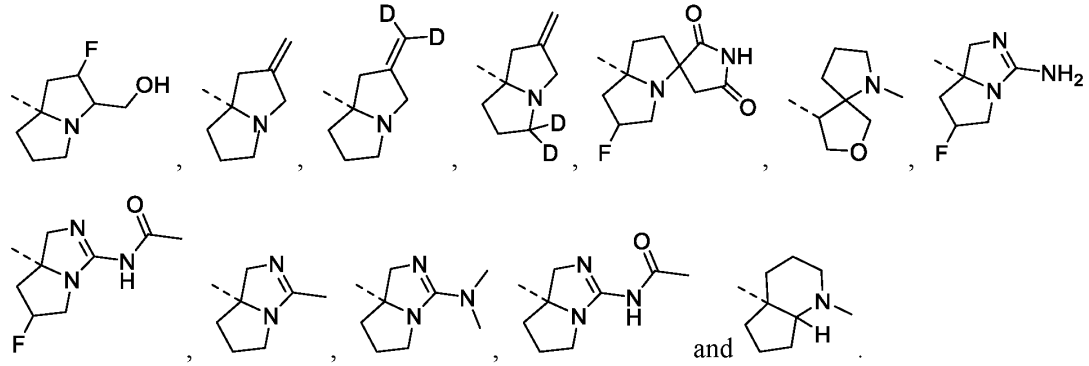
In some embodiments, R_8 is selected from H and F.

In some embodiments, R_9 is selected from -C(=O)-NH_2, -C(=O)-$NHCH_3$, -C(=O)-$N(CH_3)_2$ and -CH_2OH.

In some embodiments, R_{10} is independently selected from D, F, NH_2, CH_3, -$N(CH_3)_2$, and -NH-C(=O)-CH_3.

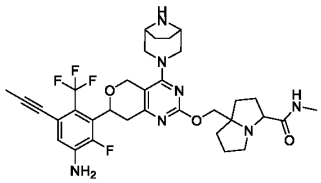
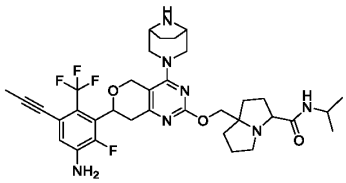
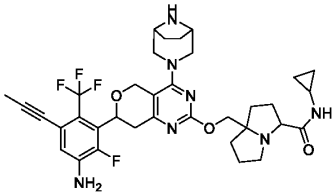
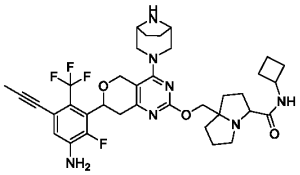
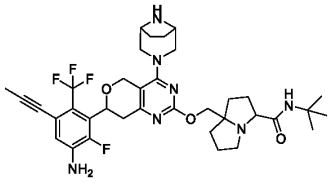
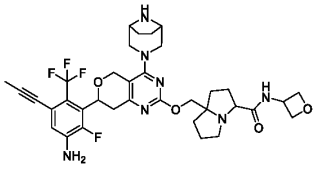
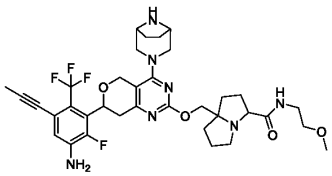
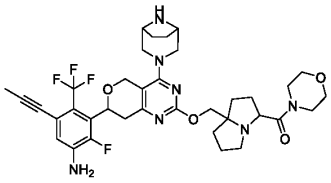
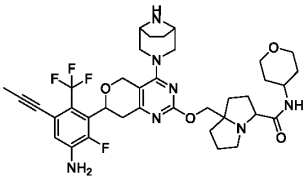
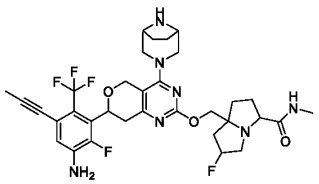
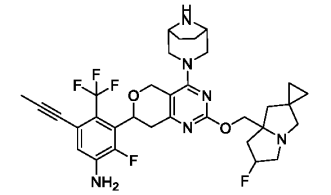
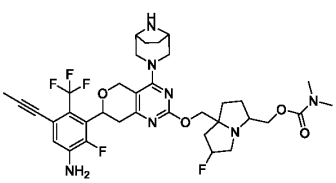
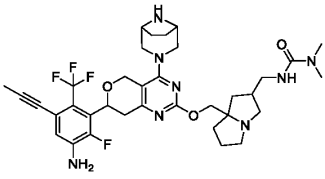
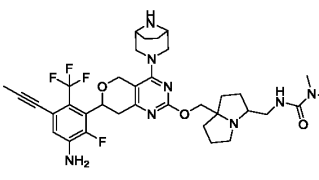
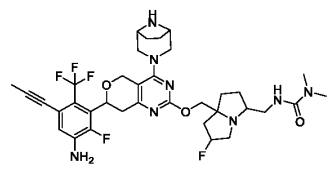
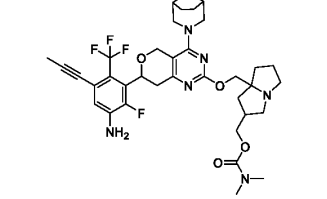
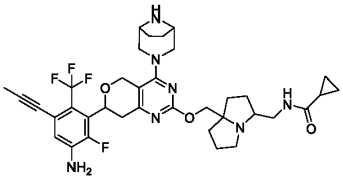
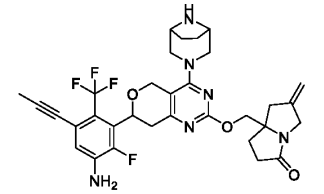
In some embodiments, ring B is selected from , , , , , , ,  and , wherein the , , ,  and  are each independently optionally substituted with 1, 2, 3, or 4 R_{10}.

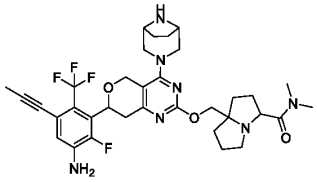
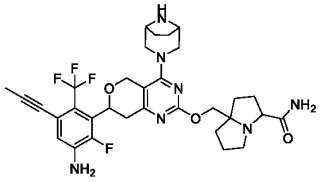
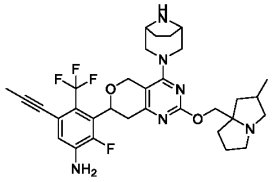
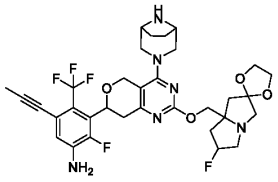
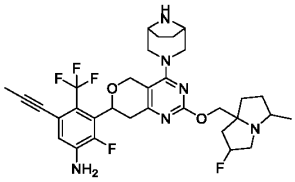
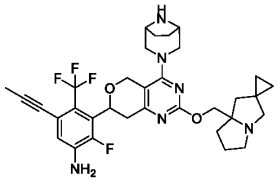
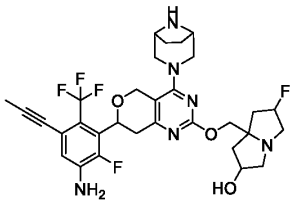
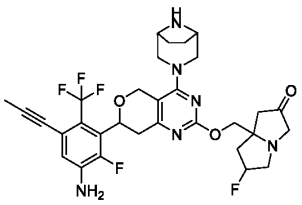
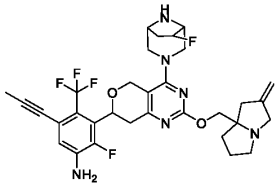
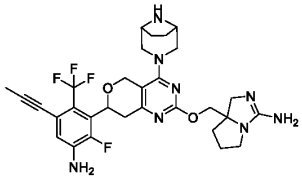
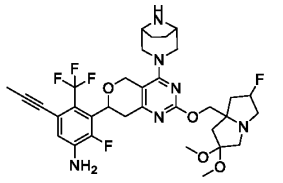
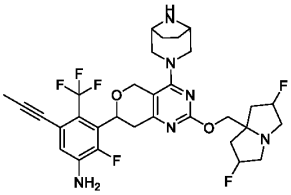
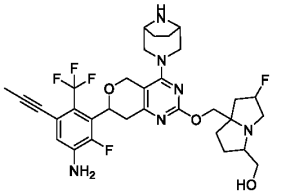
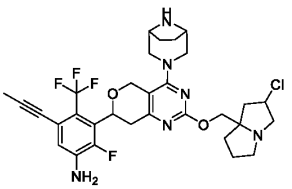
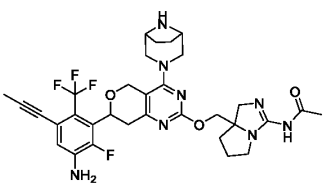
In some embodiments, ring B is selected from , , ,

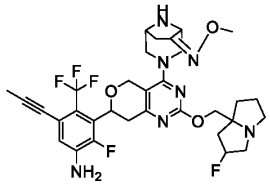
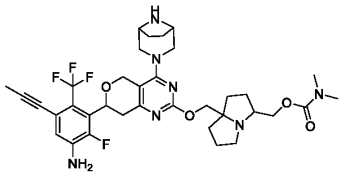
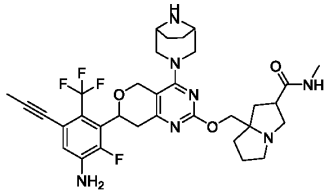
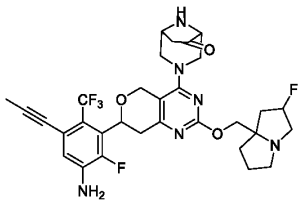
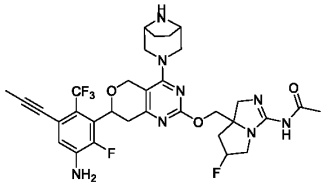
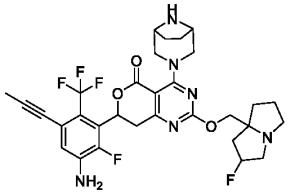
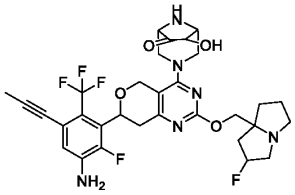
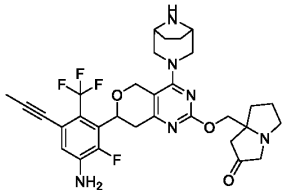
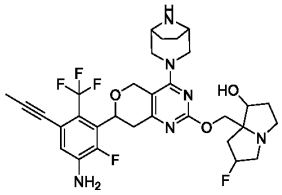
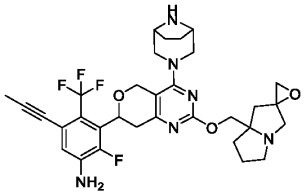
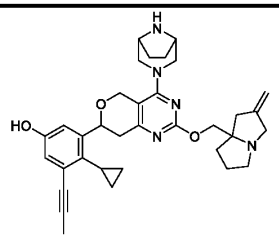
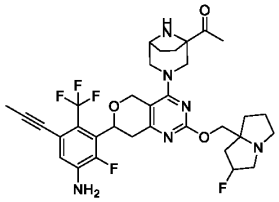
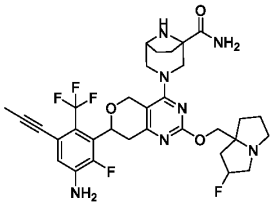
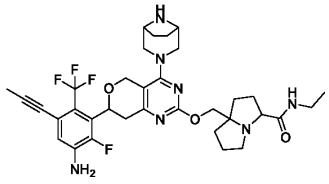
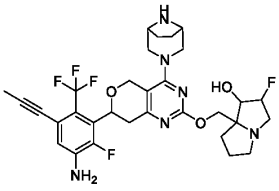
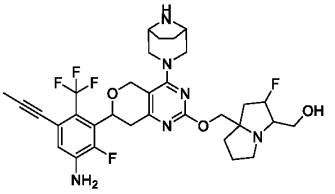
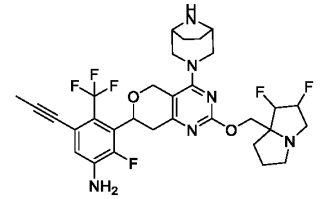


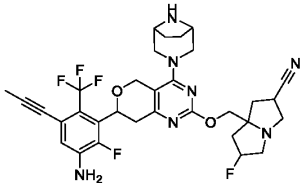
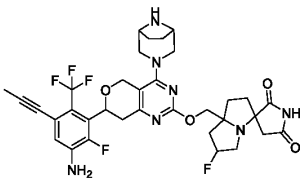
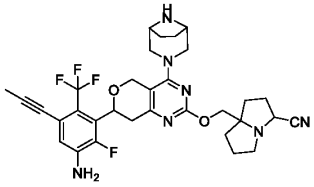
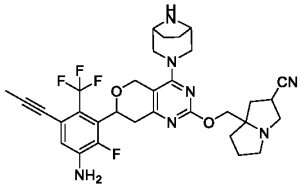
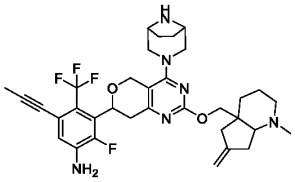
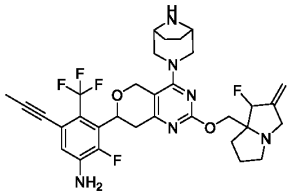
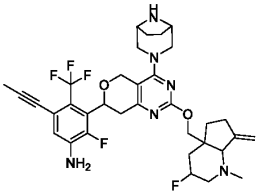
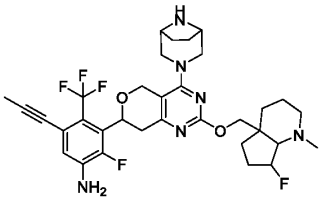
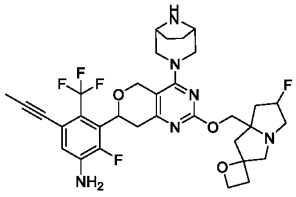
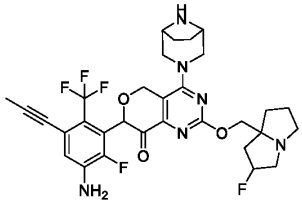
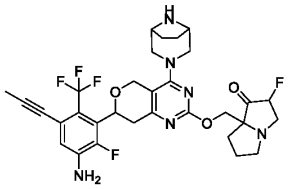
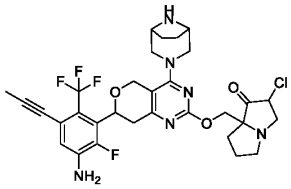
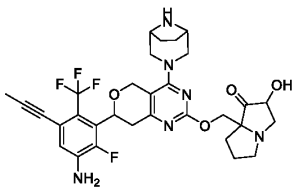
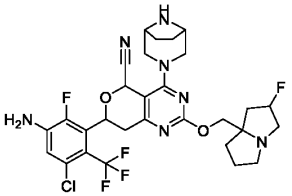
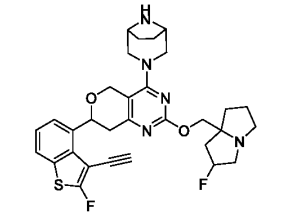
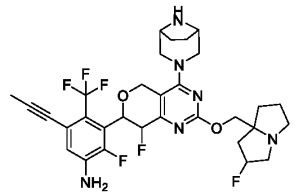
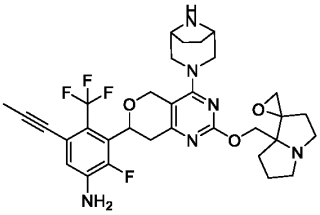
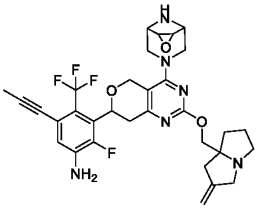
In some embodiments, the compound of Formula (I'') is a compound of Tables 1, 2, 2a, 3, 4, 5, 5a, 6, or 6a, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

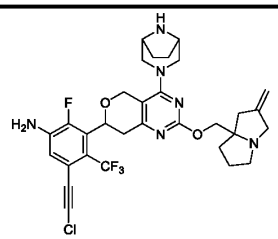
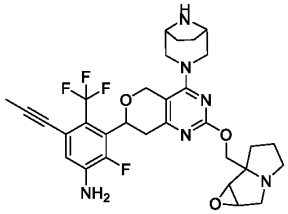
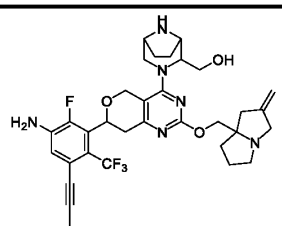
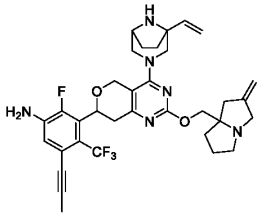
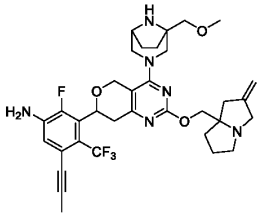
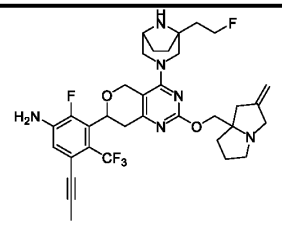
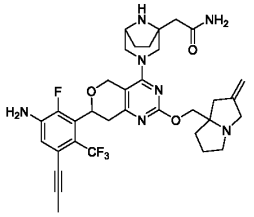
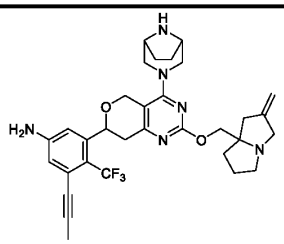
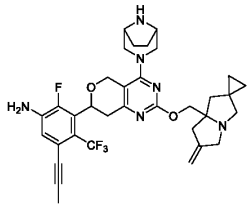
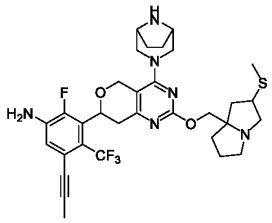
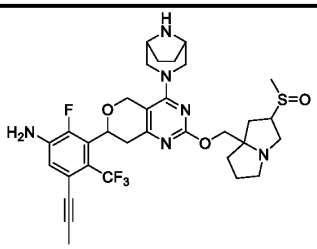
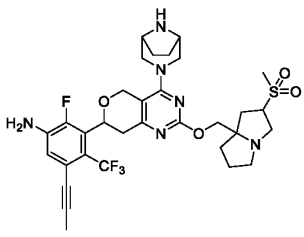
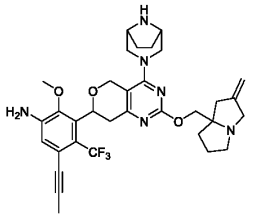
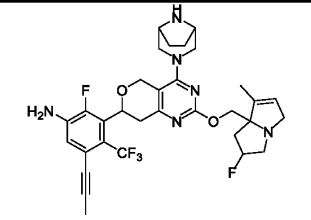
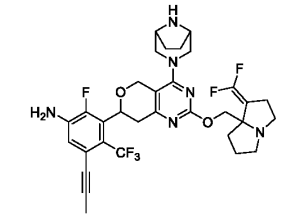
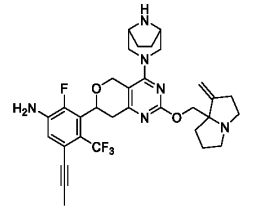
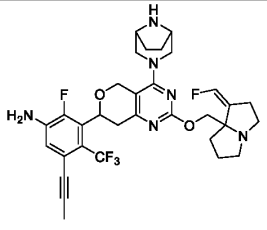
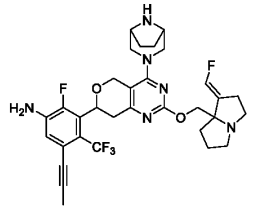
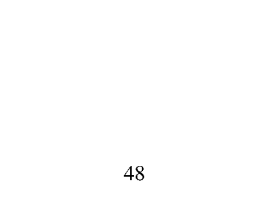
Table 1

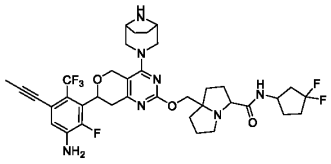
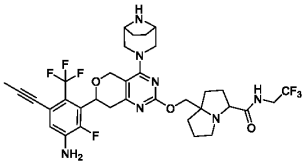
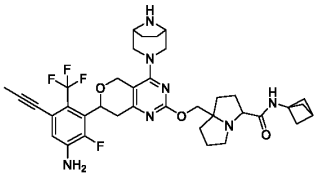
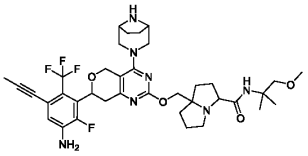
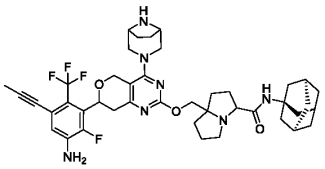
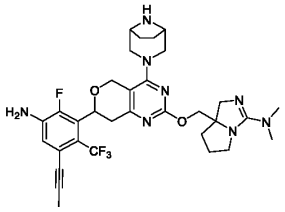
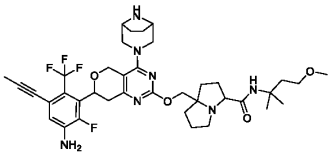
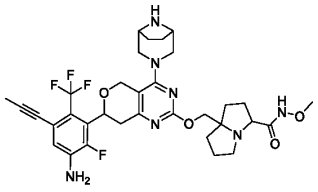
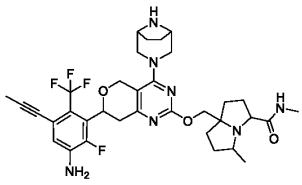
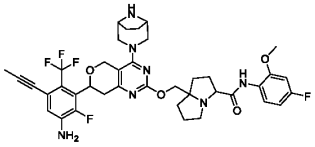
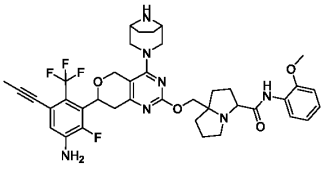
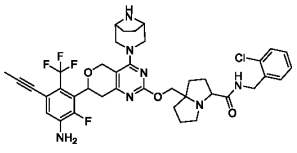
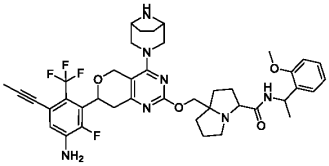
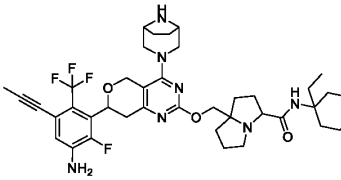
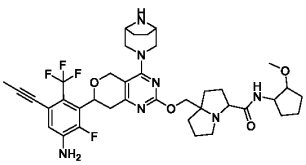
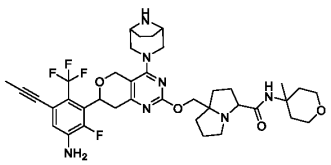
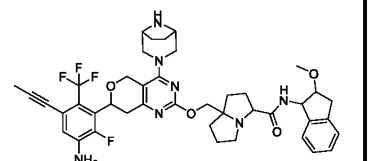
		
		
		
		
		
		

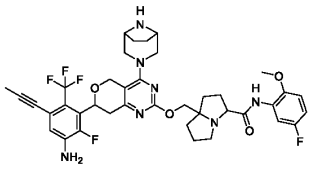
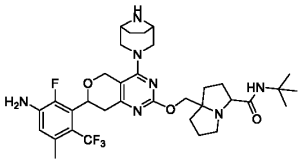
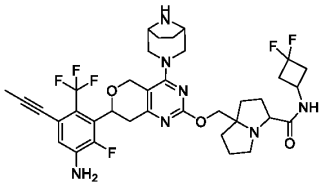
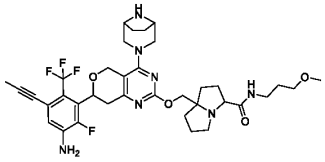
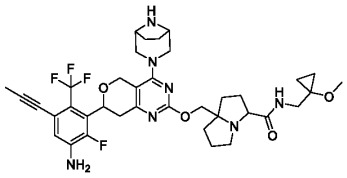
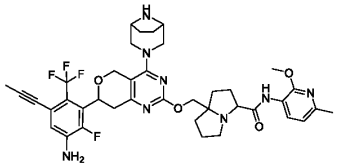
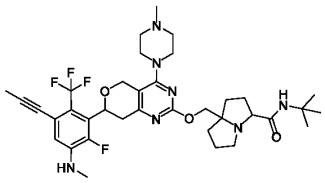
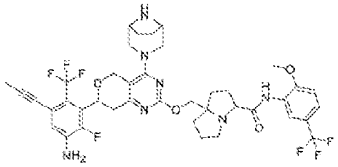
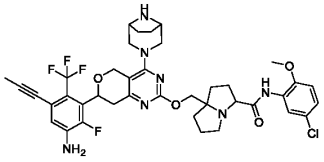
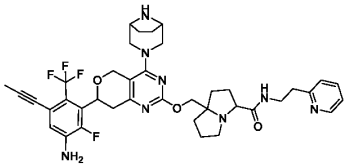
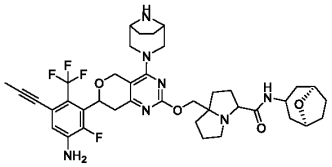
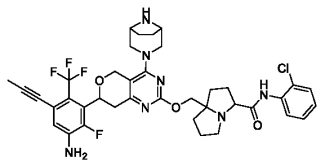
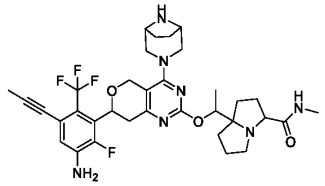
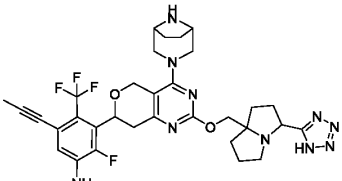
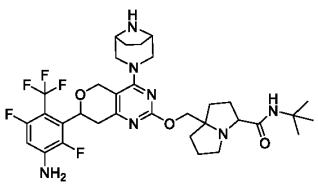
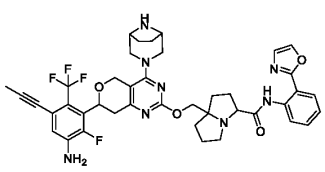
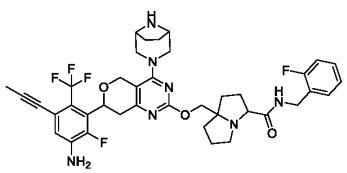
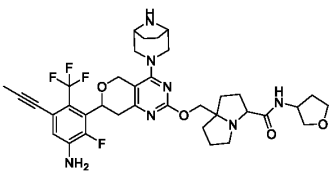
		
		
		
		
		

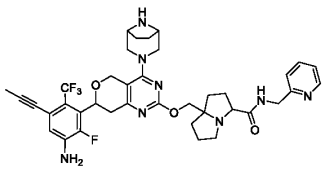
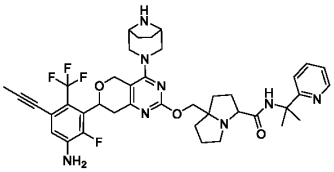
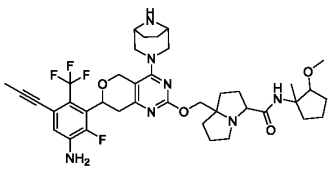
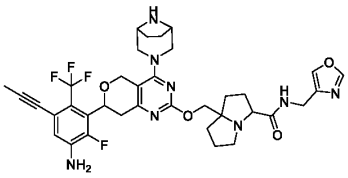
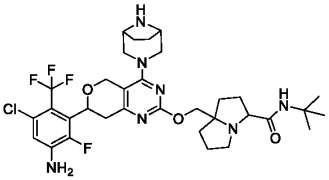
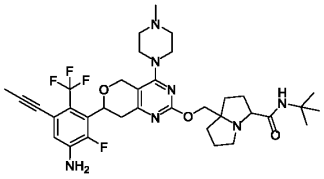
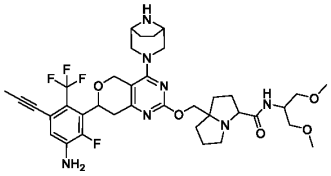
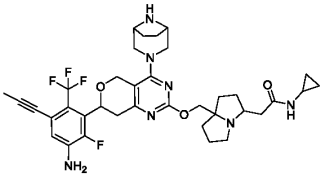
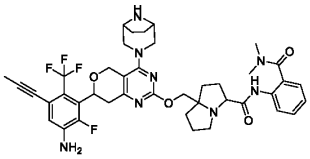
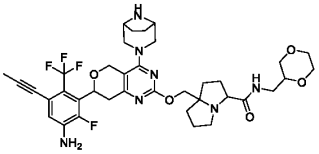
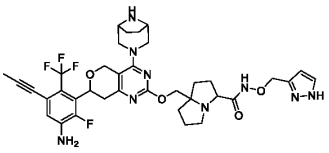
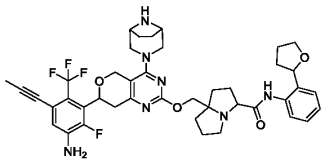
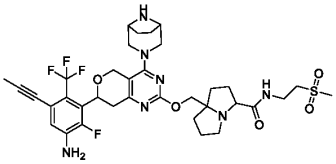
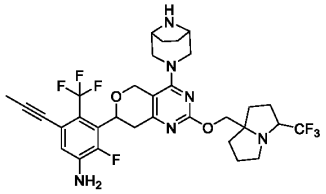
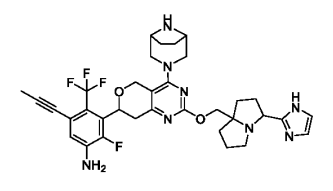
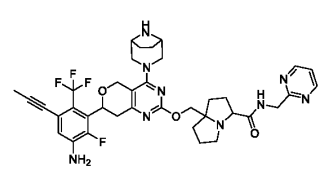
		
		
		
	--	
		
		

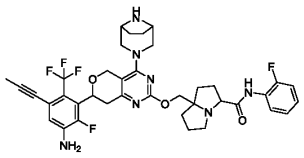
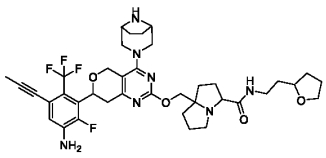
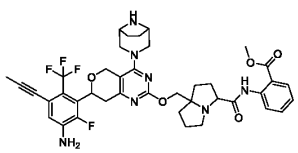
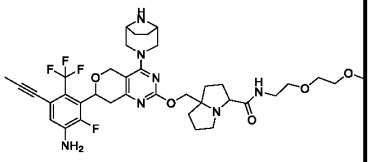
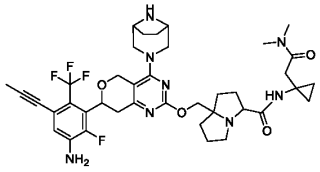
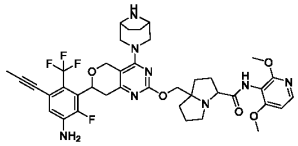
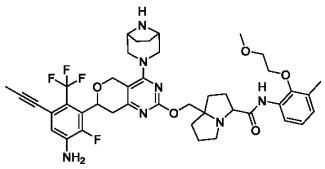
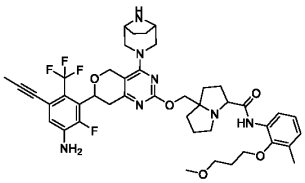
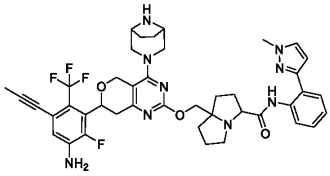
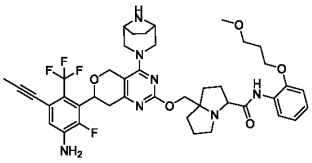
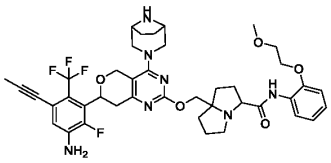
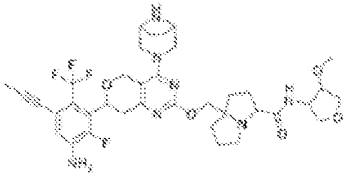
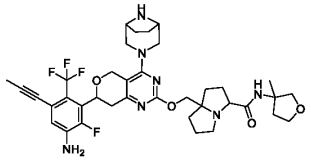
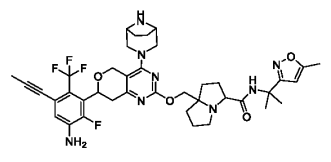
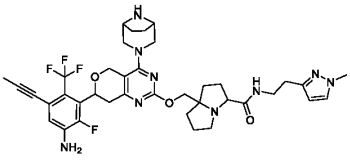
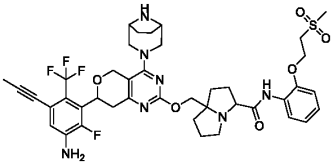
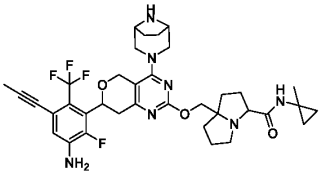
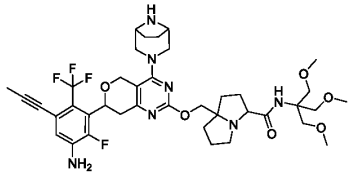
		
		
		
		
		
		

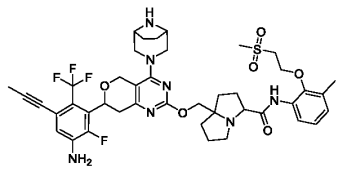
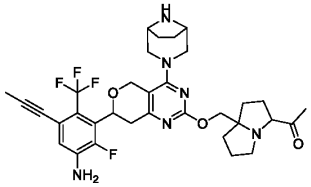
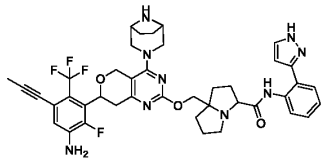
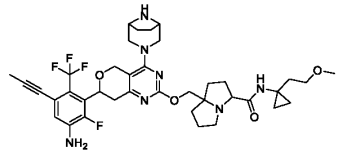
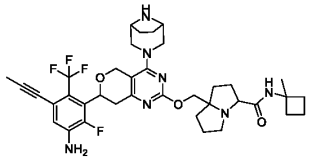
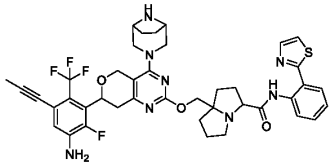
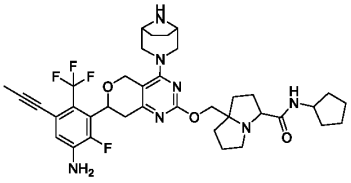
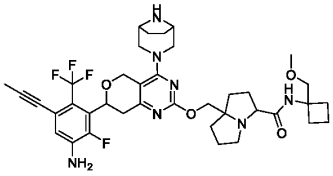
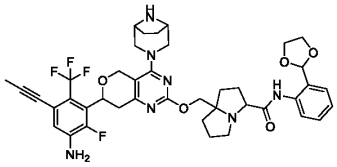
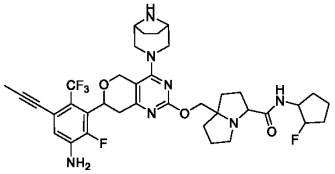
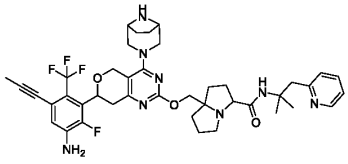
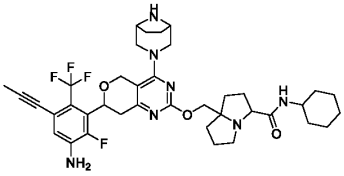
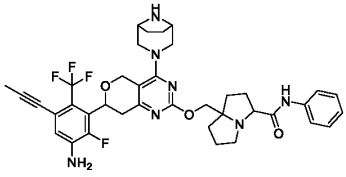
		
		
		
		
		
		
		

		
	--	
		
		
		
		

		
		
--		
		
		--
		

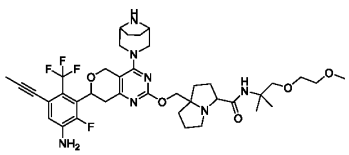
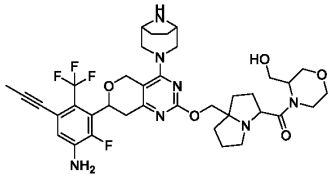
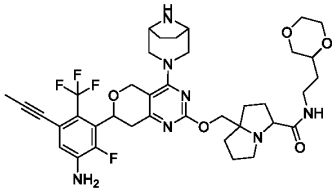
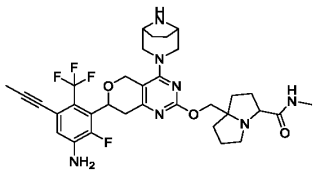
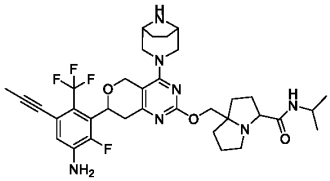
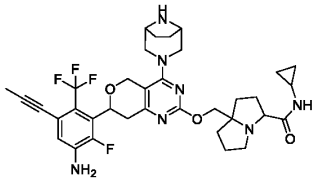
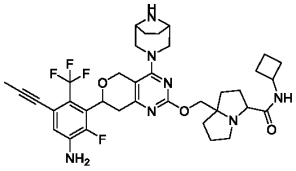
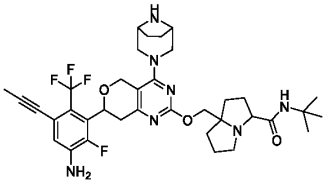
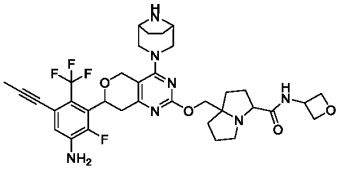
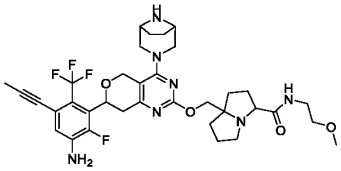
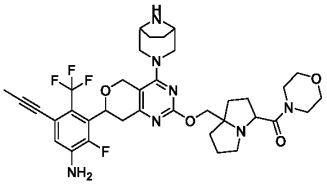
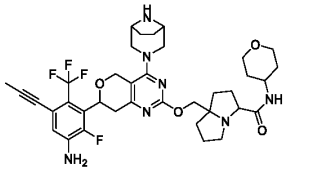
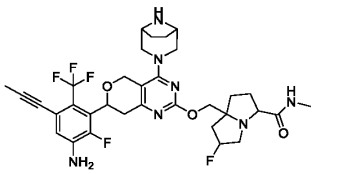
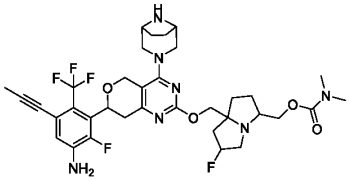
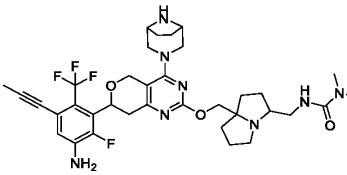
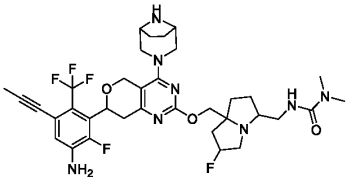
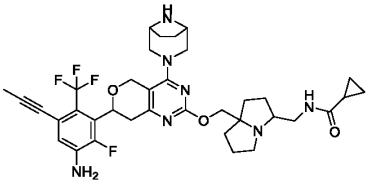
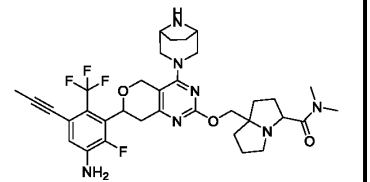
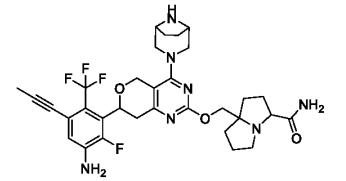
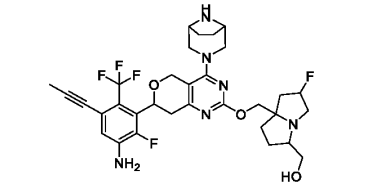
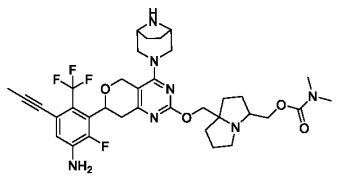
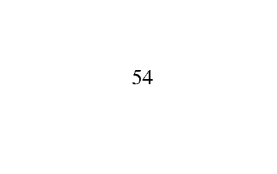
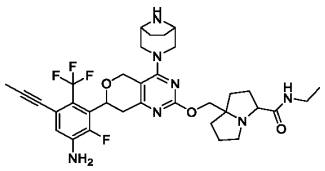
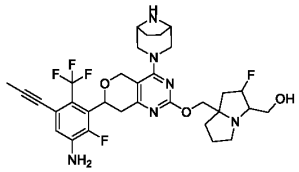
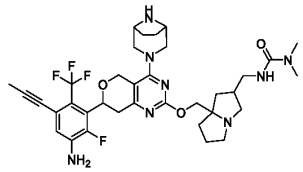
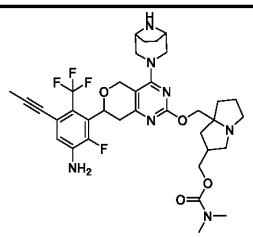
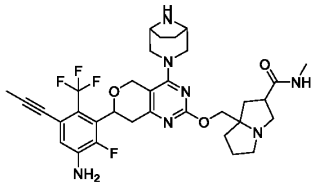
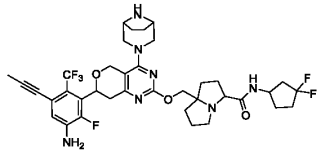
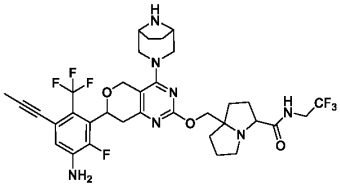
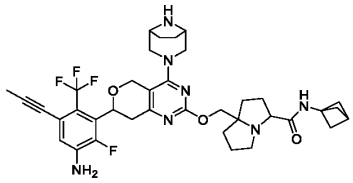
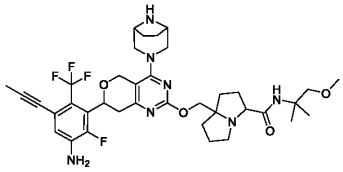
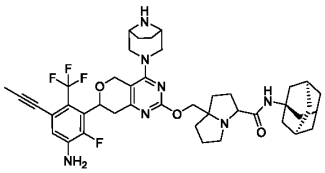
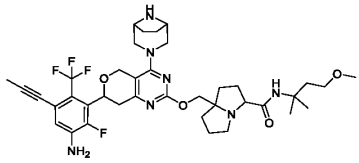
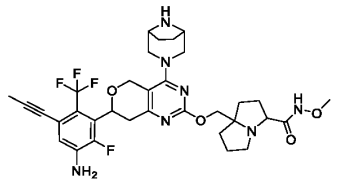
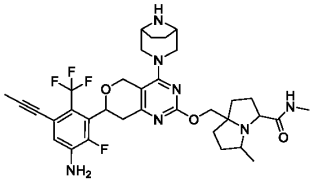
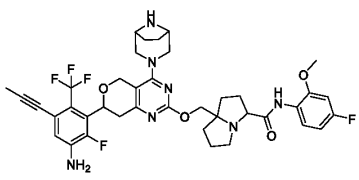
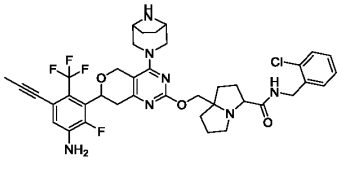
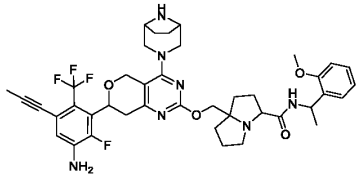
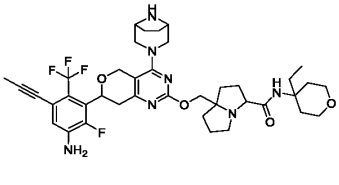
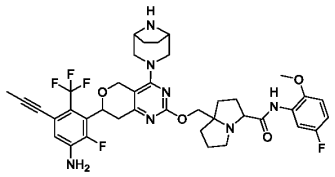
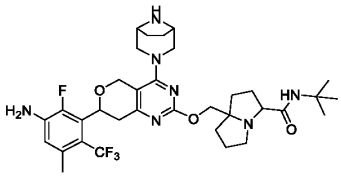
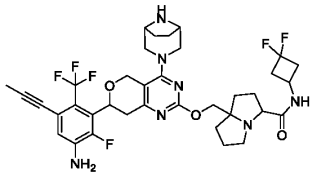
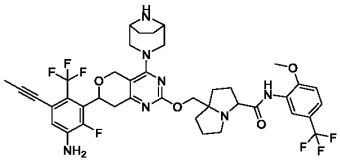
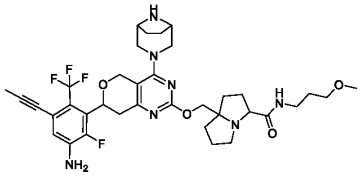
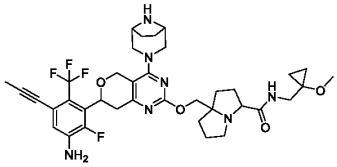
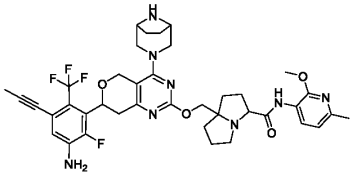
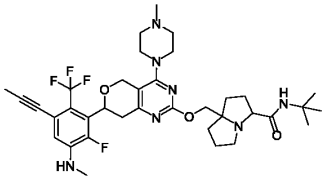
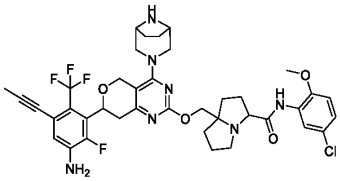
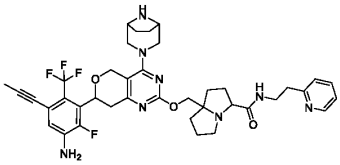
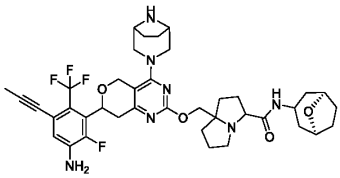
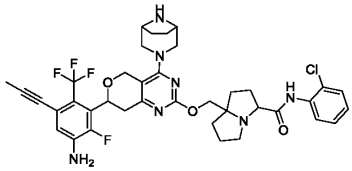
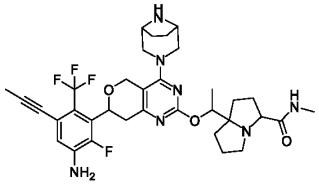
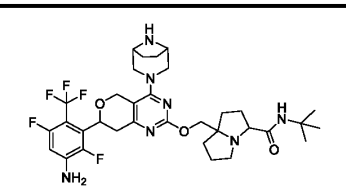
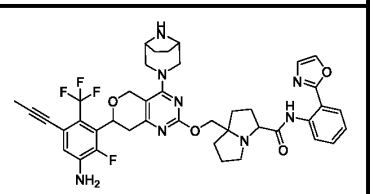
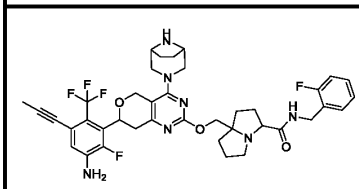
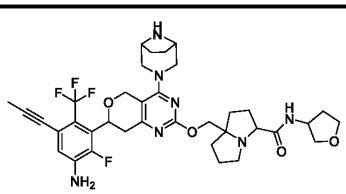
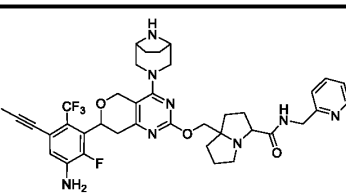
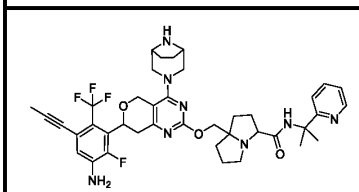
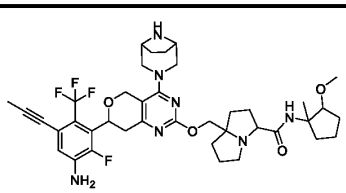
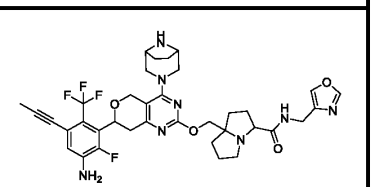
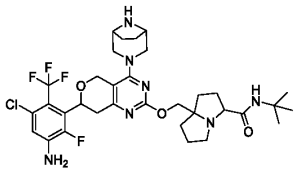
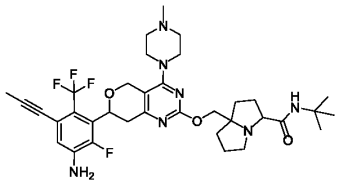
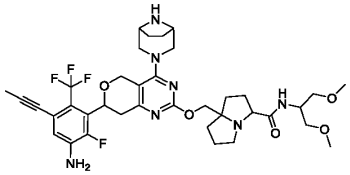
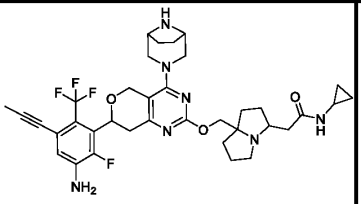
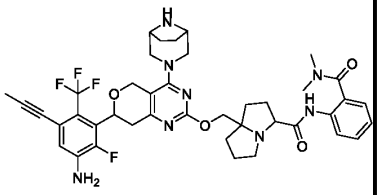
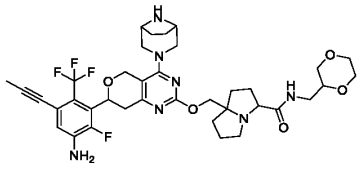
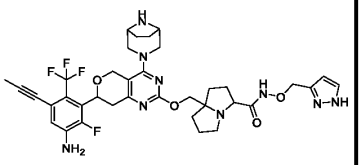
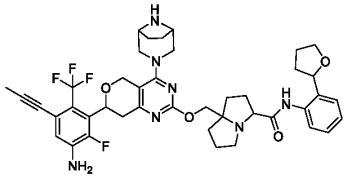
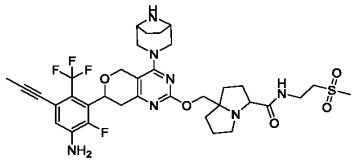
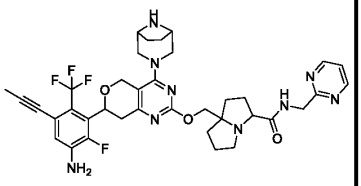
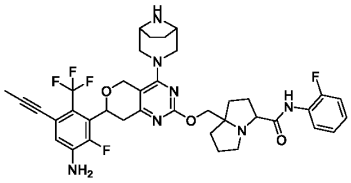
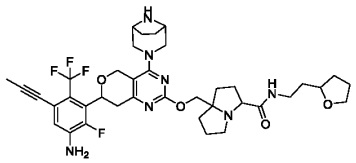
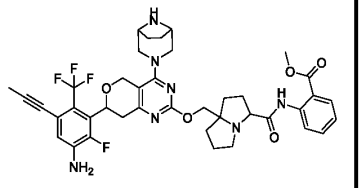
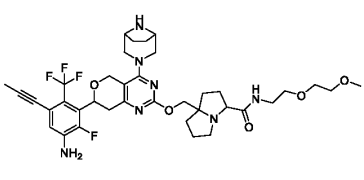
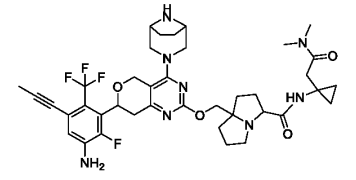
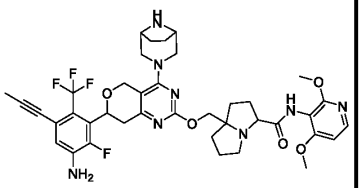
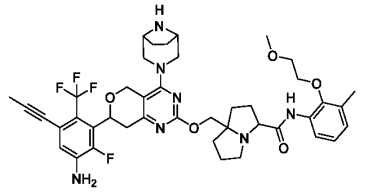
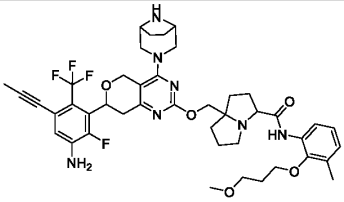
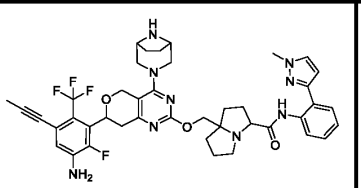
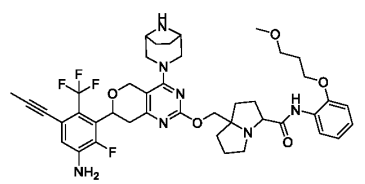
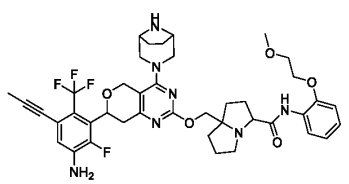
		

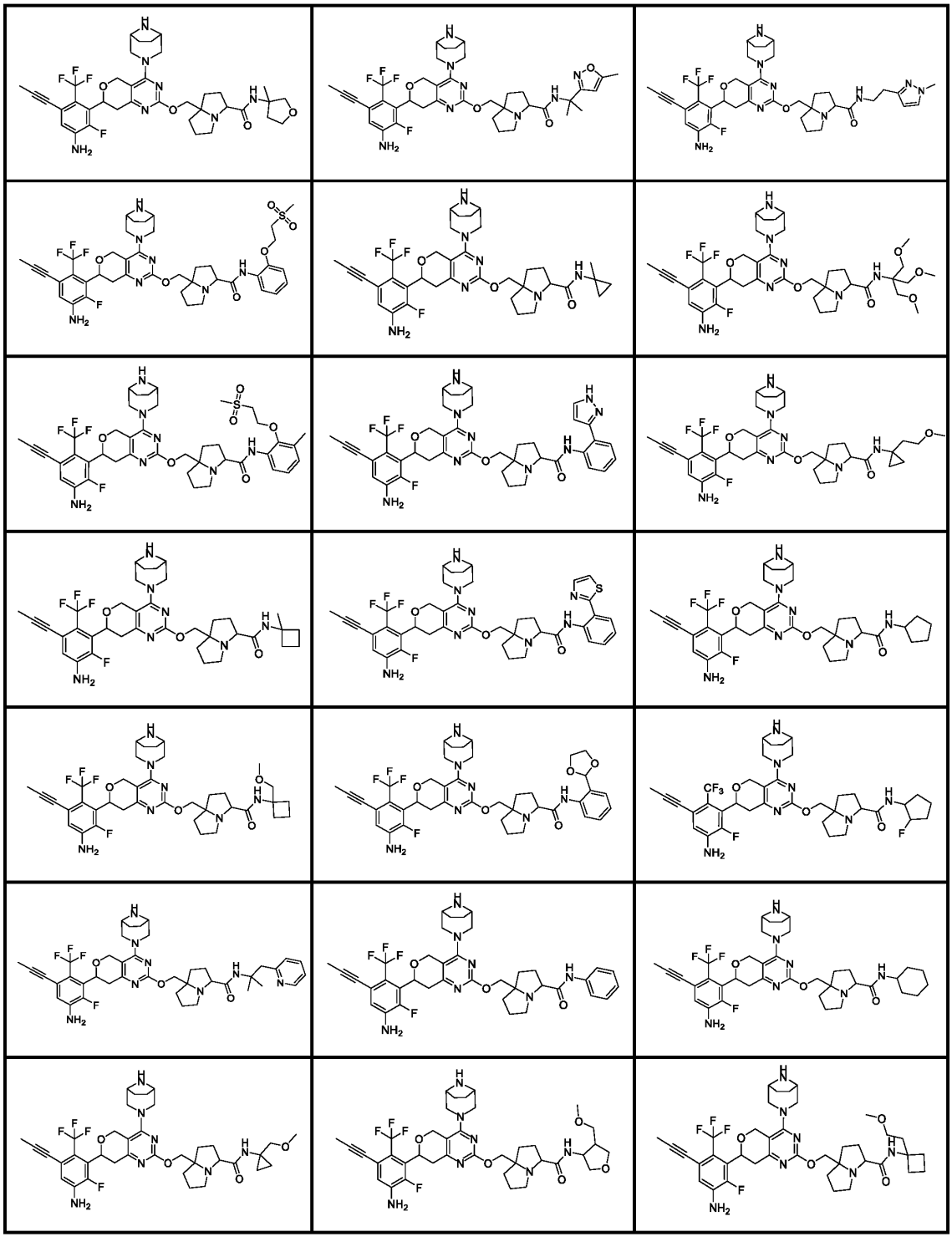
Table 2



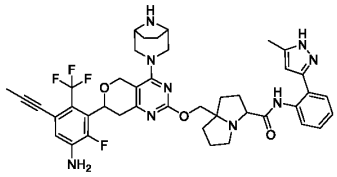
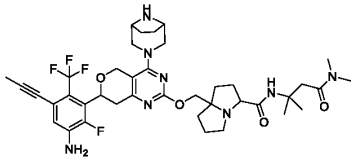
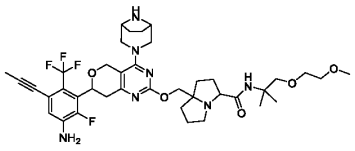
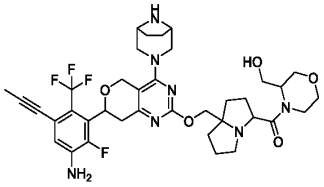
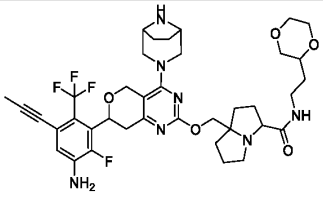
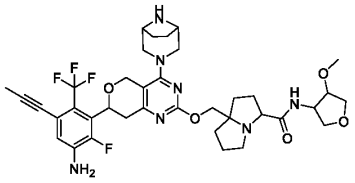
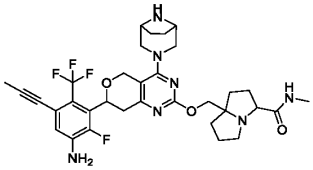
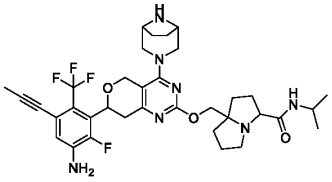
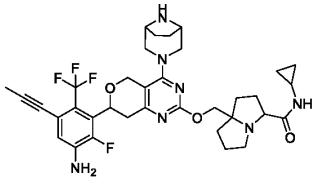
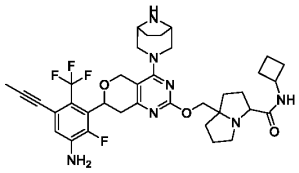
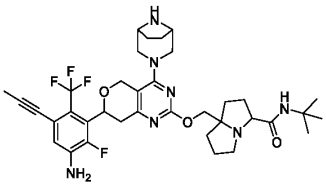
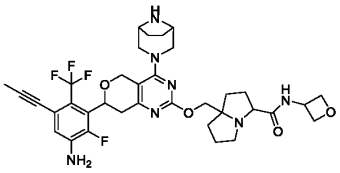
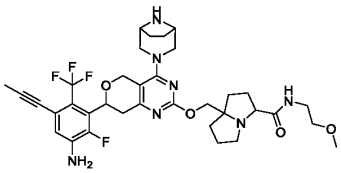
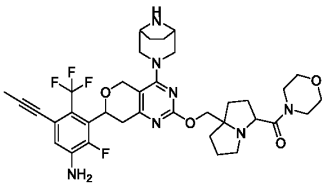
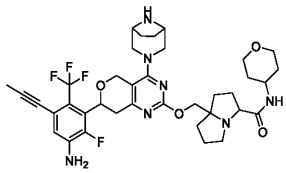
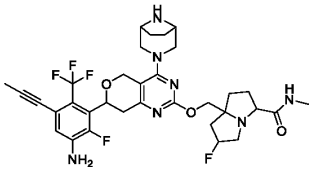
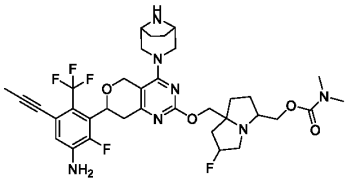
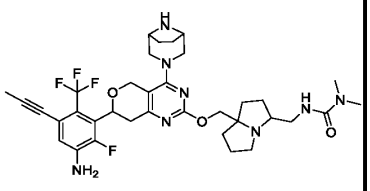
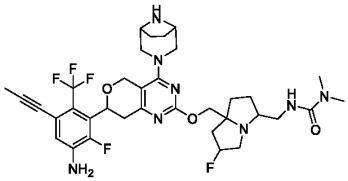
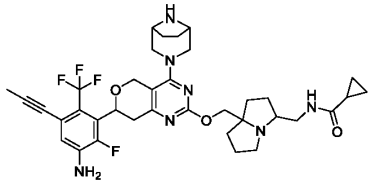
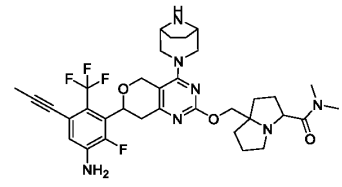
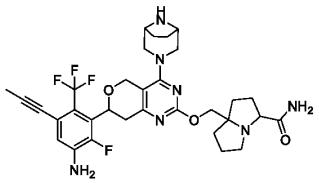
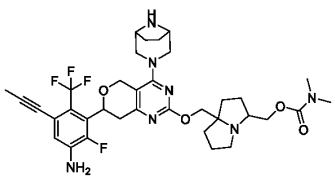
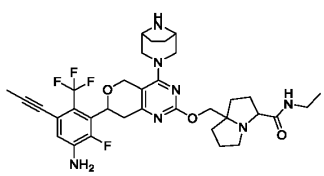
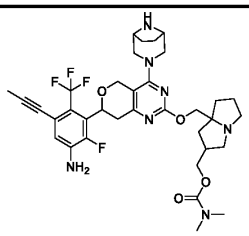
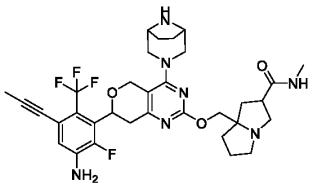
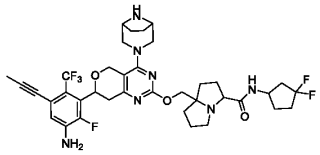
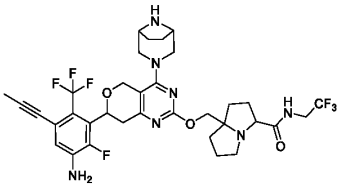
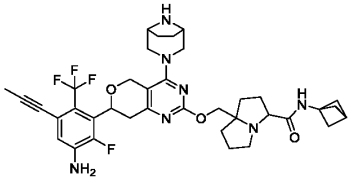
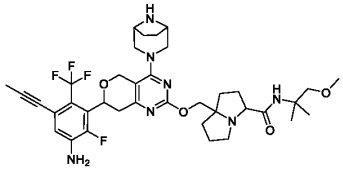
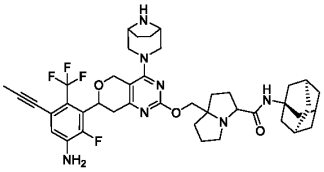
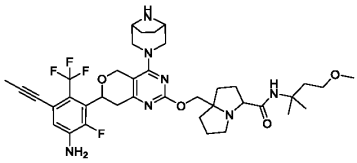
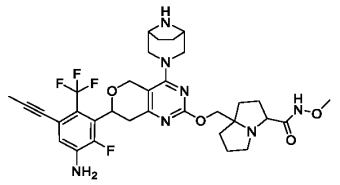
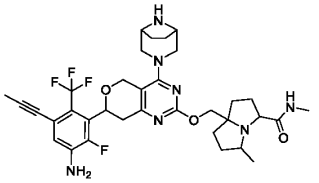
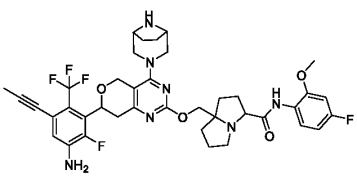
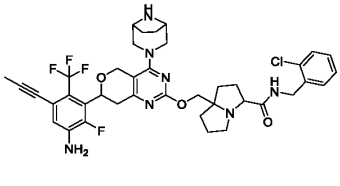
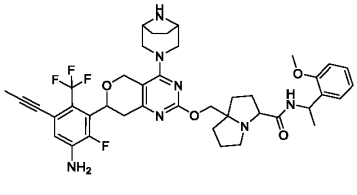
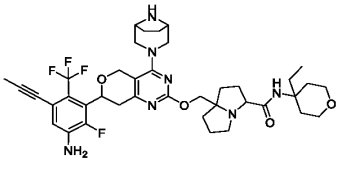
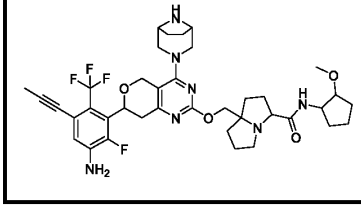
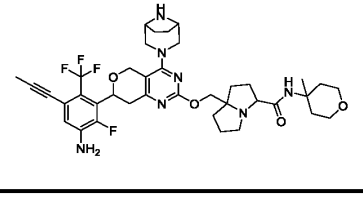
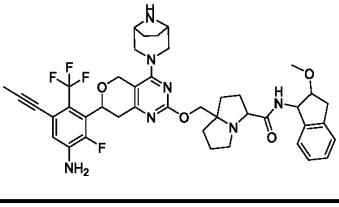
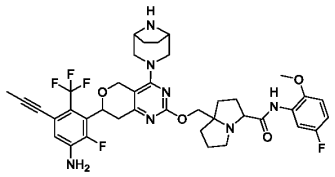
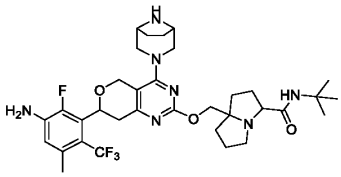
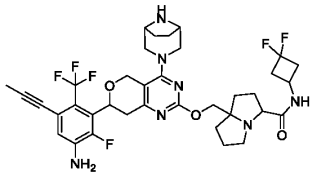
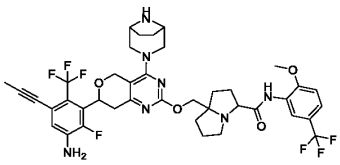
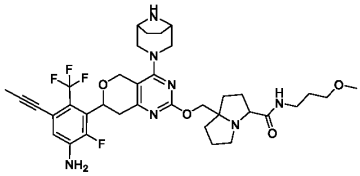
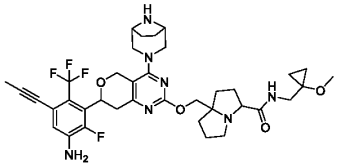
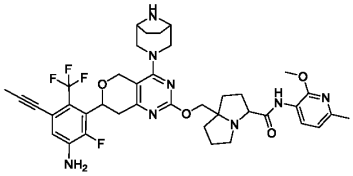
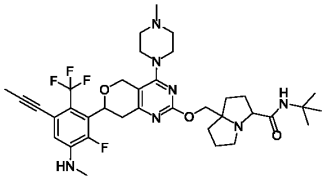
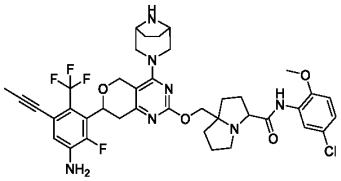
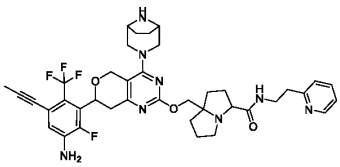
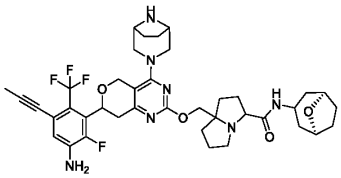
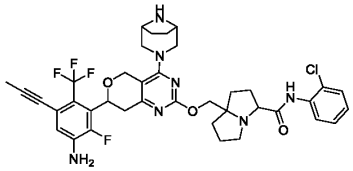
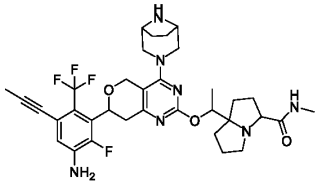
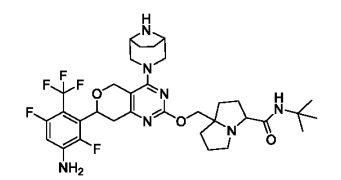
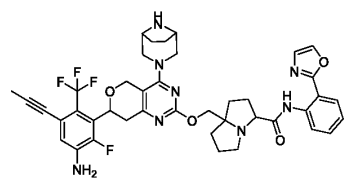
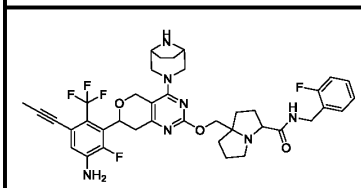
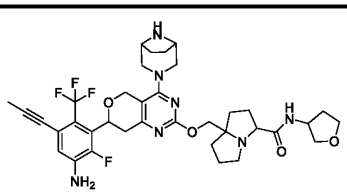
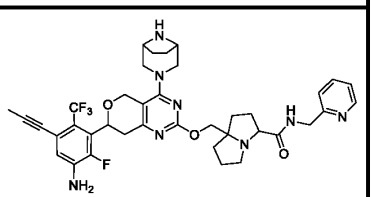
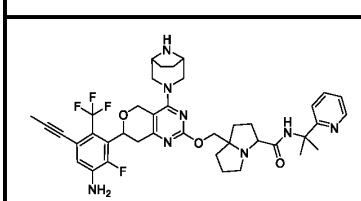
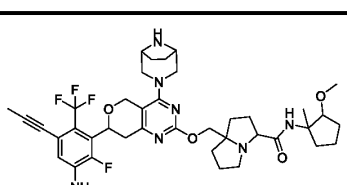
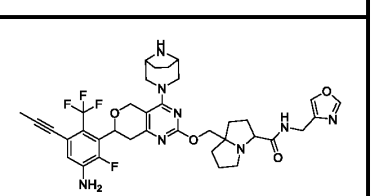
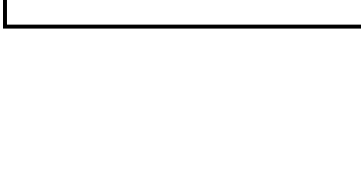
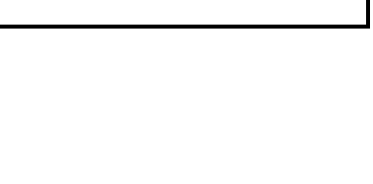
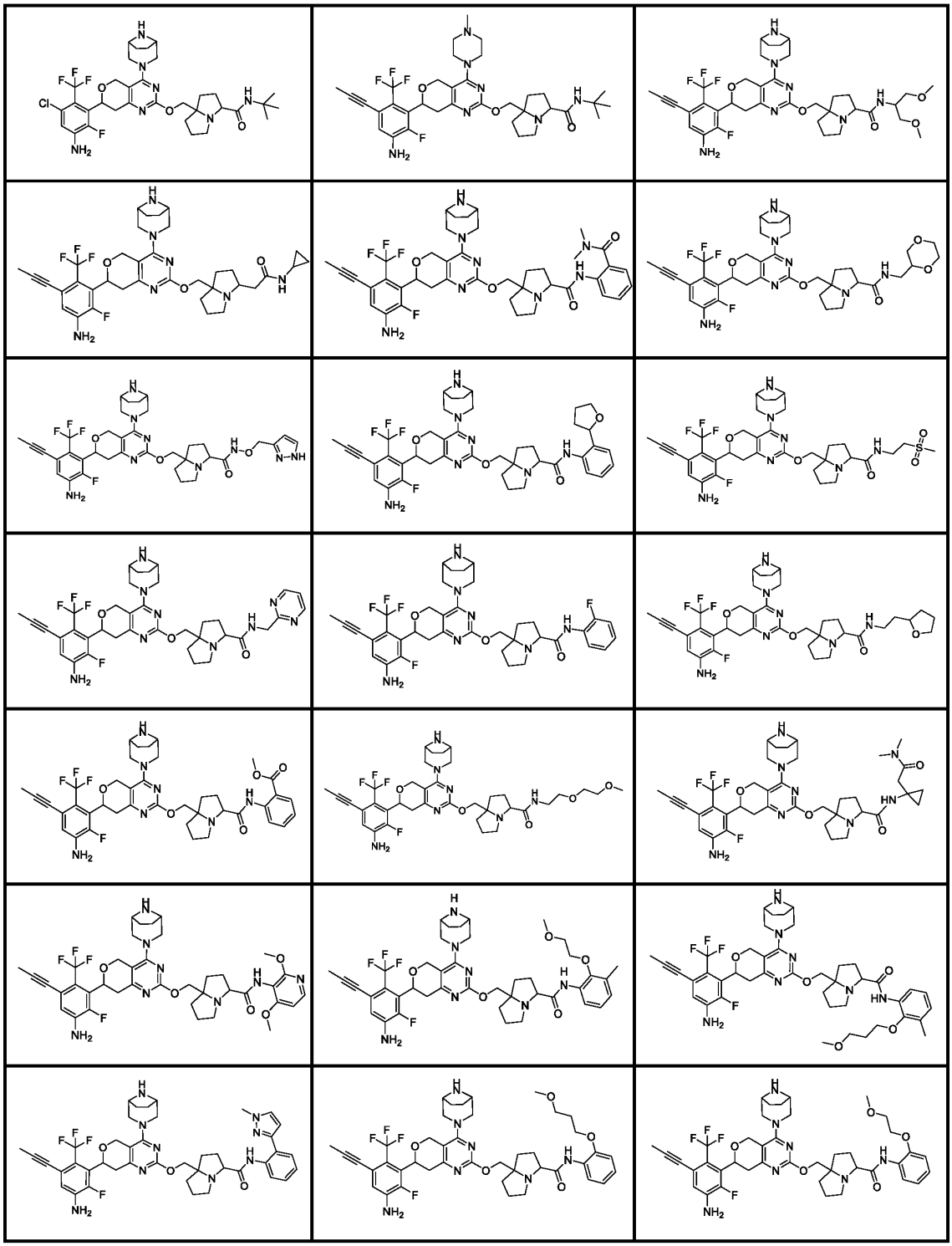
		
		

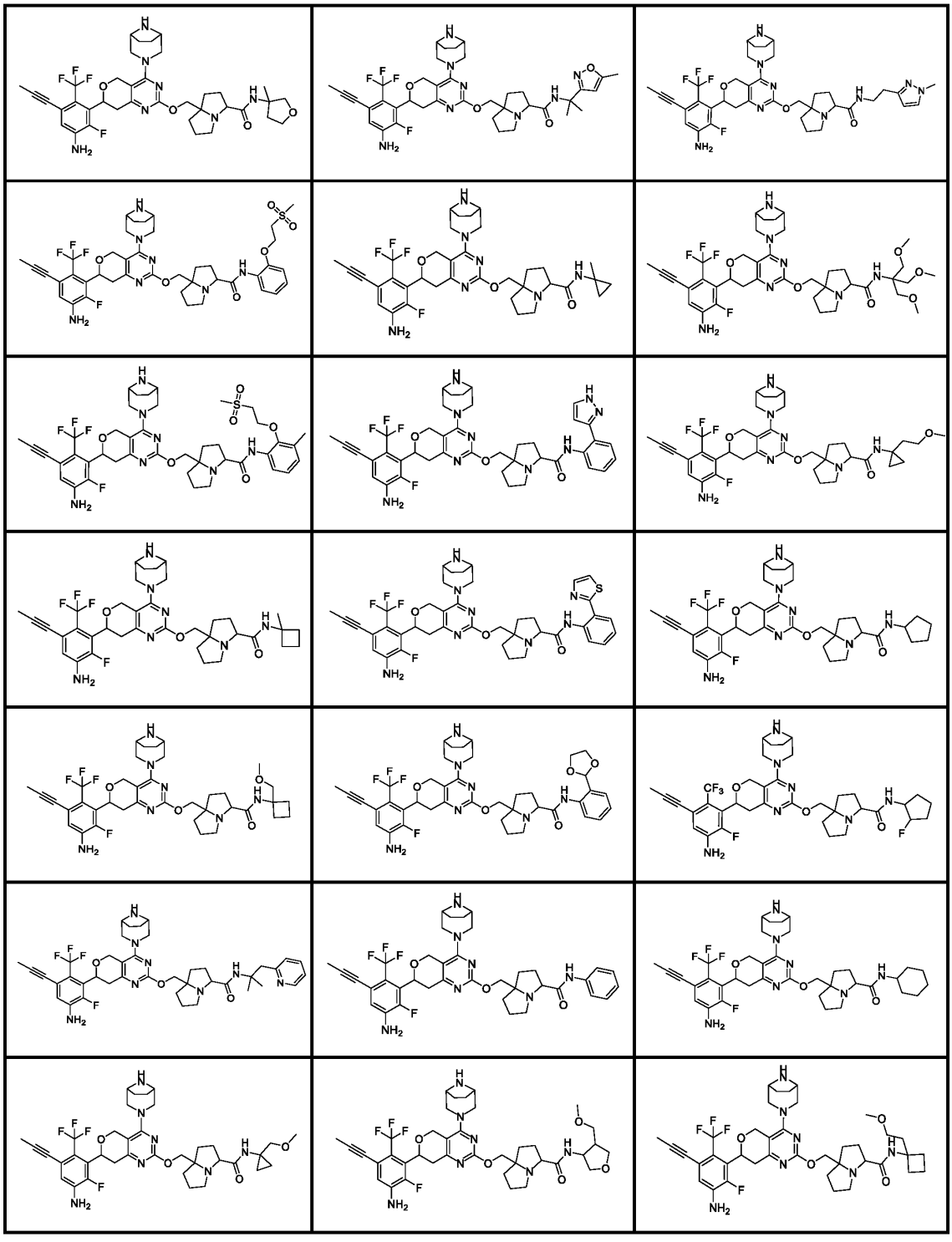
Table 2a





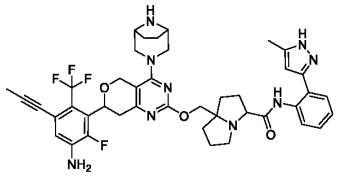
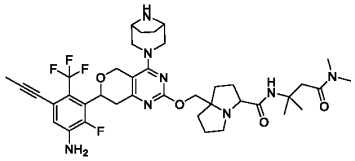
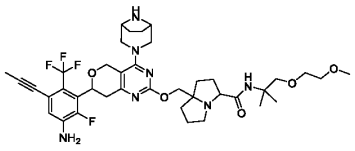
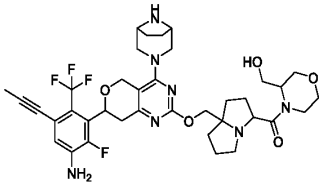
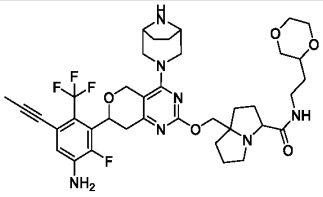
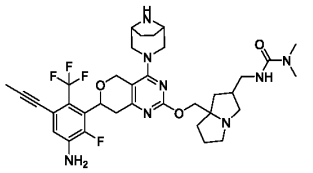
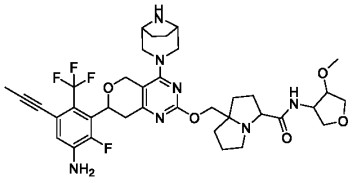
		
		
		

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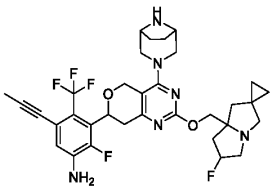
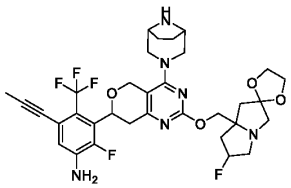
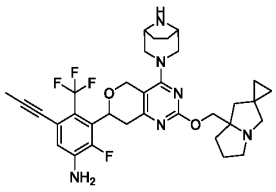
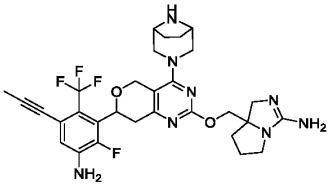
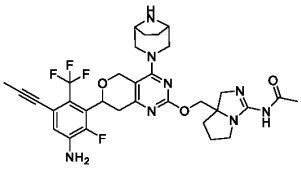
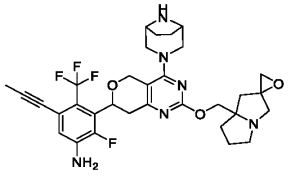
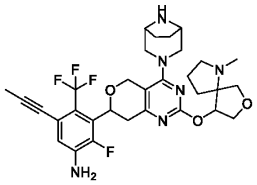
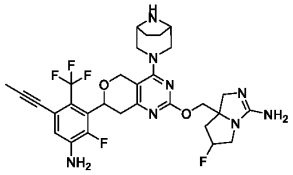
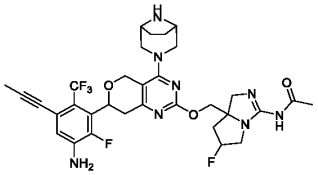
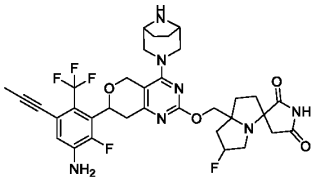
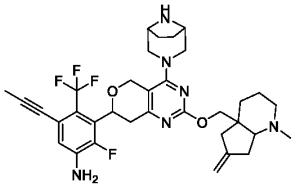
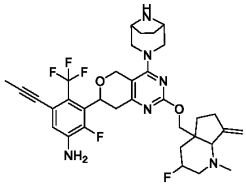
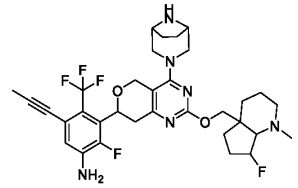
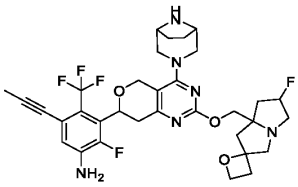
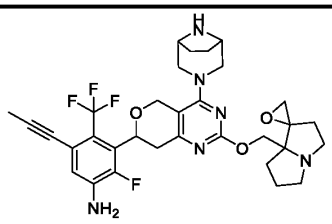
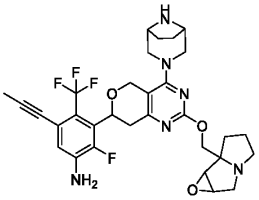
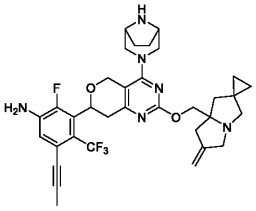
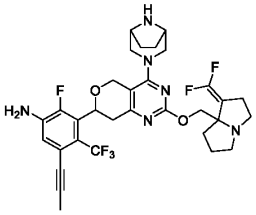
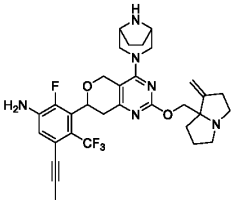
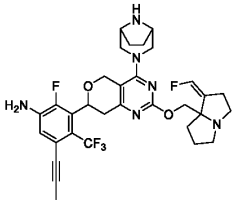
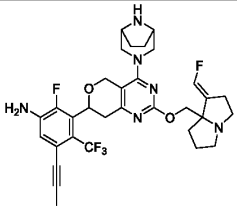
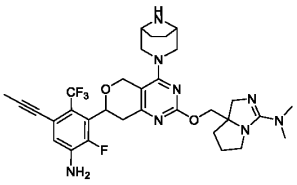
Table 3

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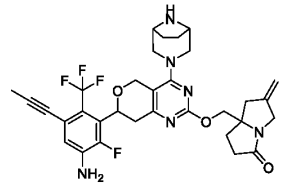	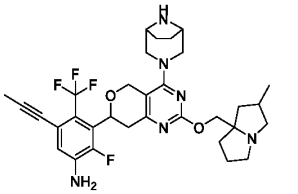	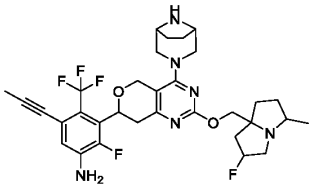
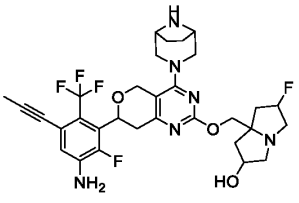	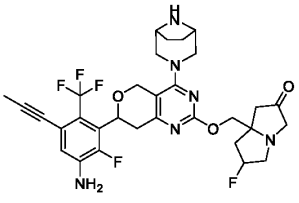	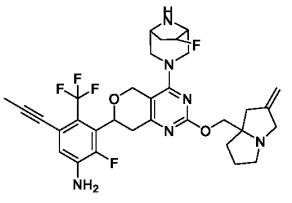
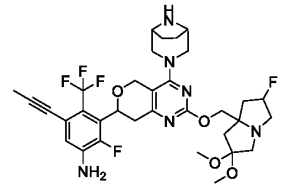	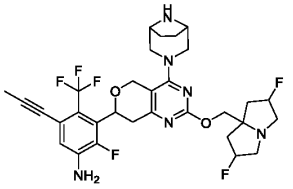	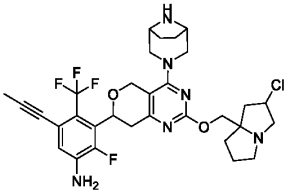

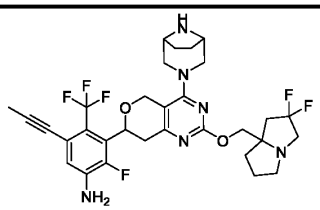	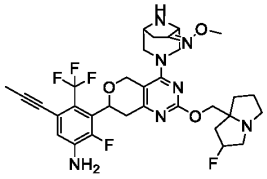	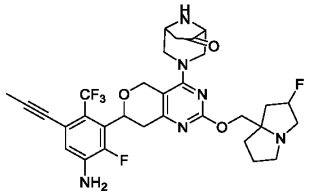
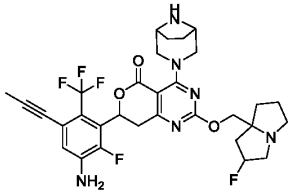	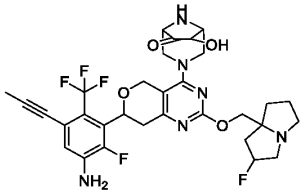	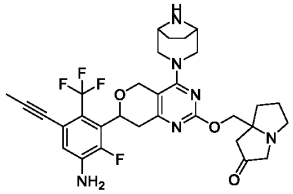
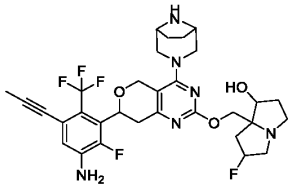	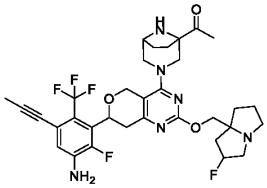	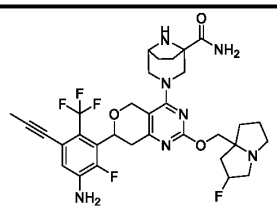
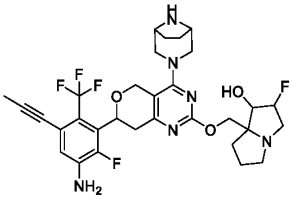	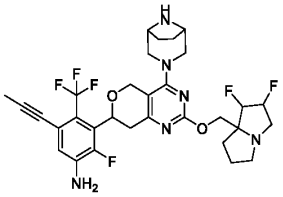	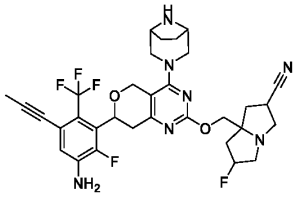
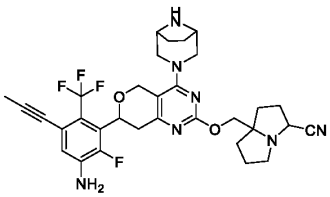	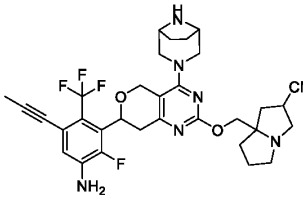	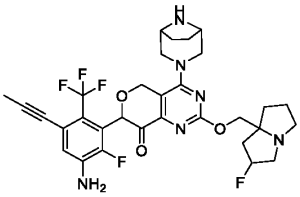
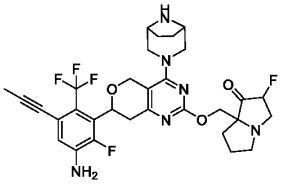		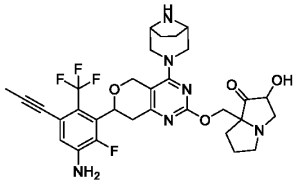
	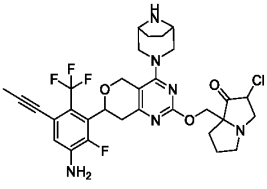	
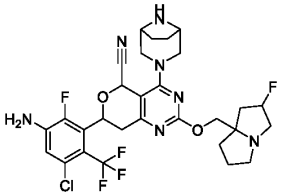	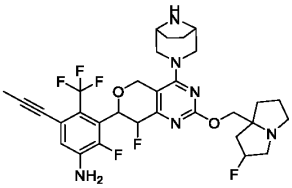	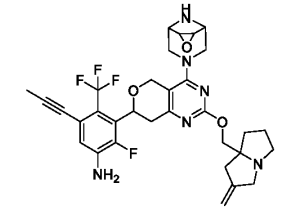

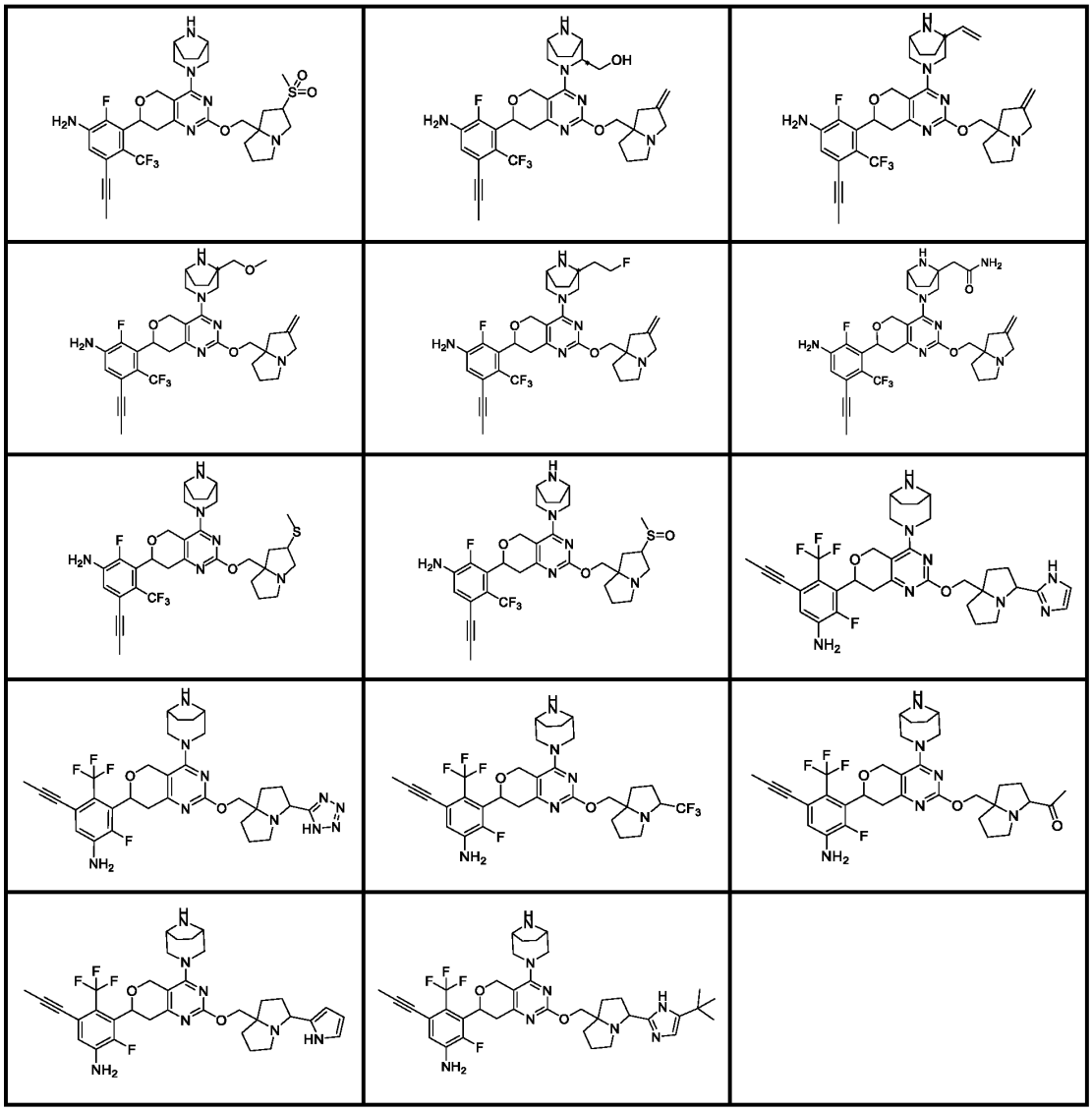

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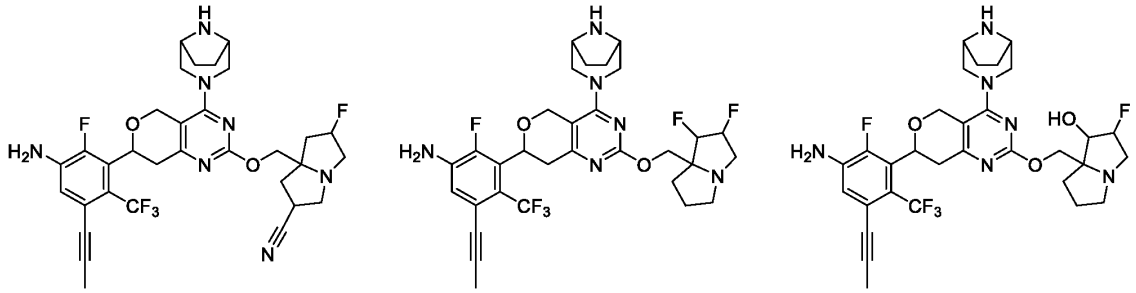

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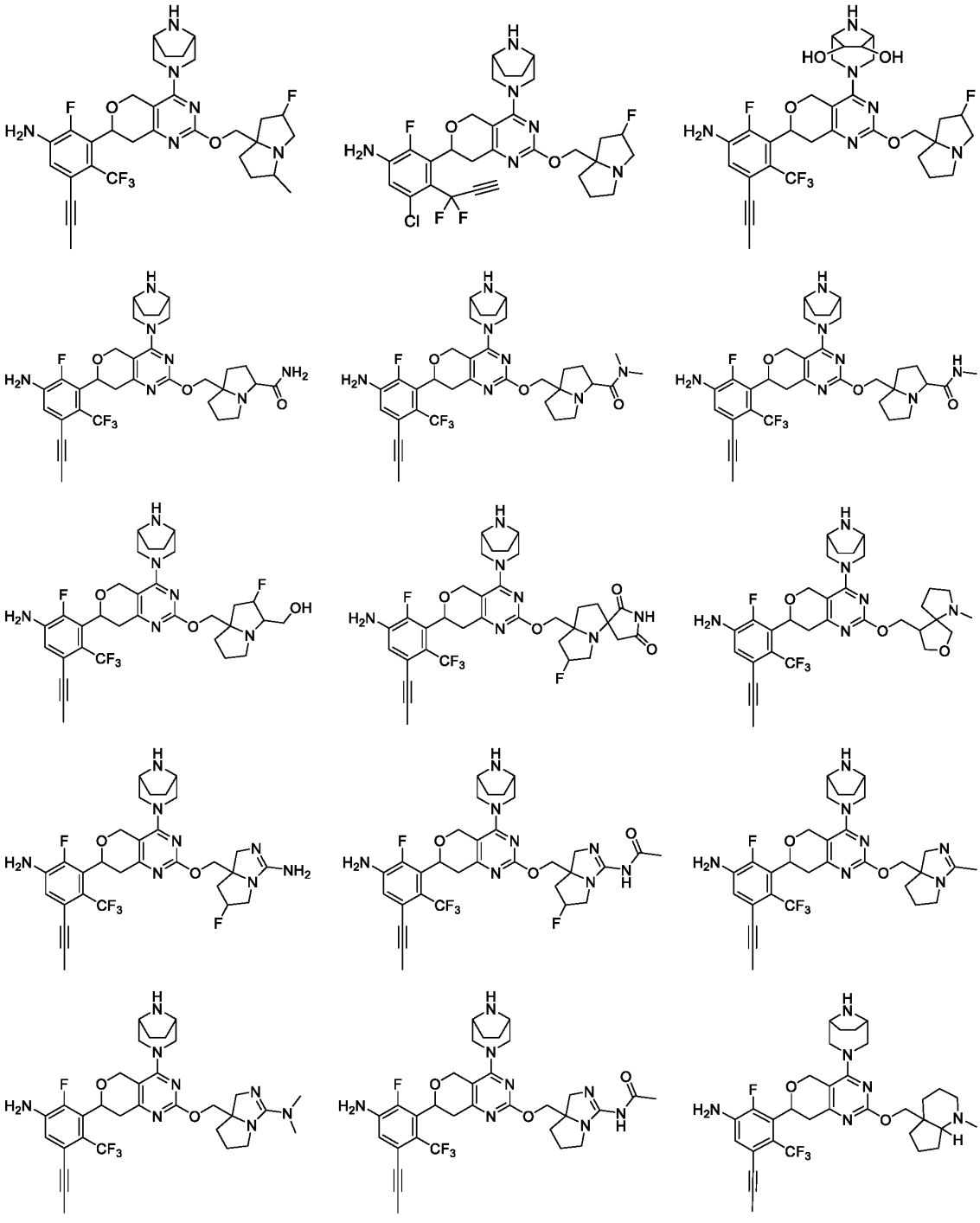
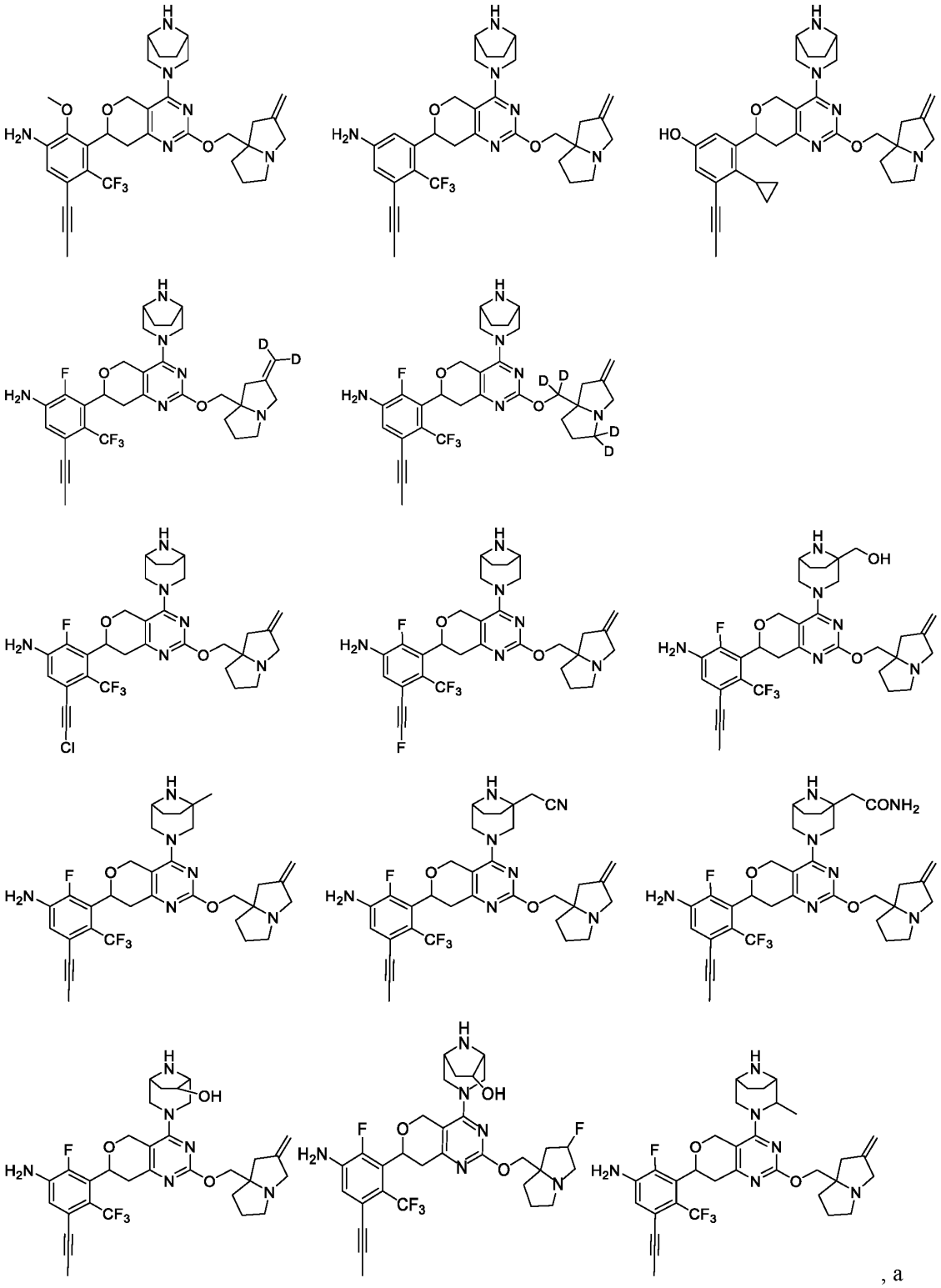
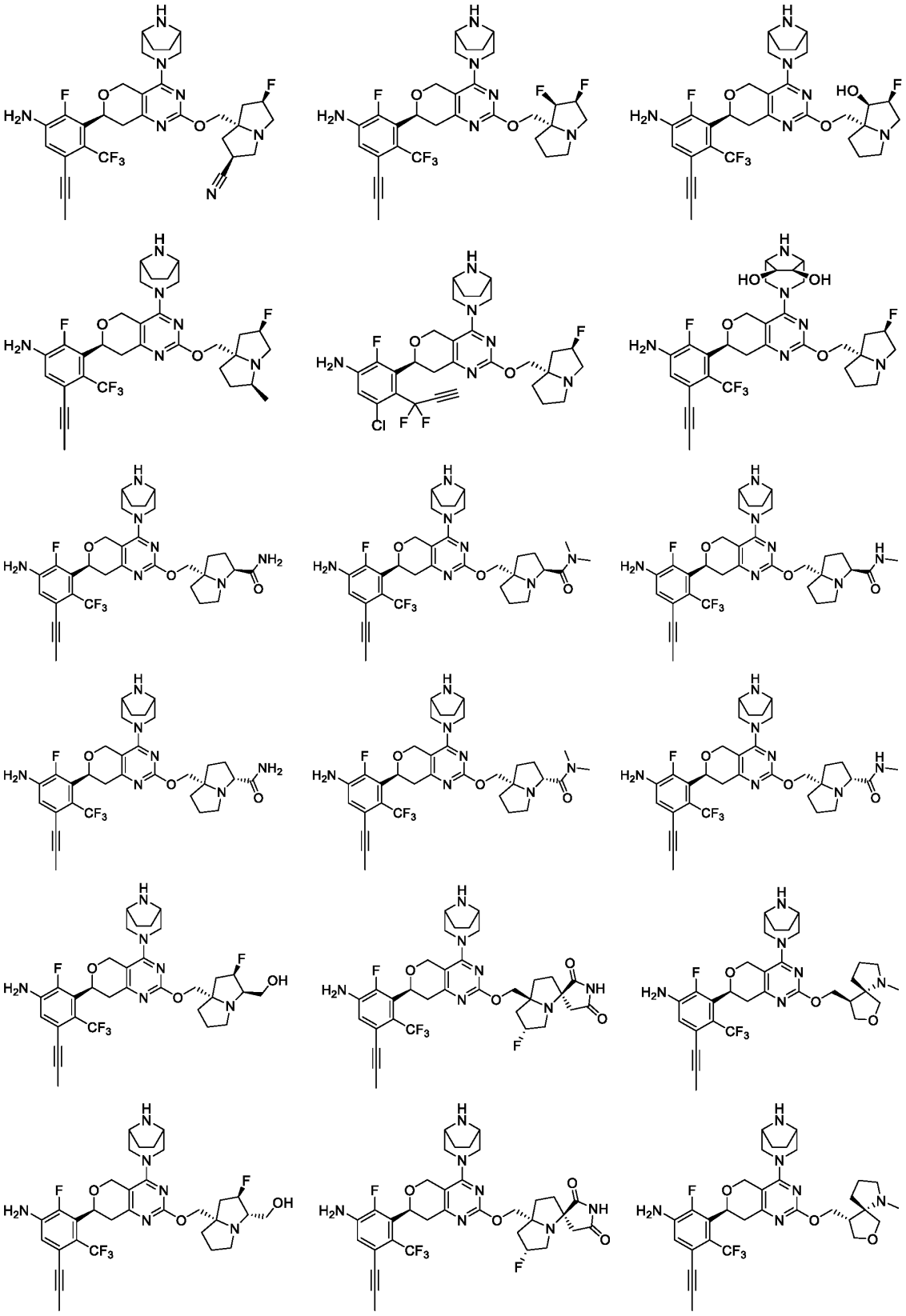


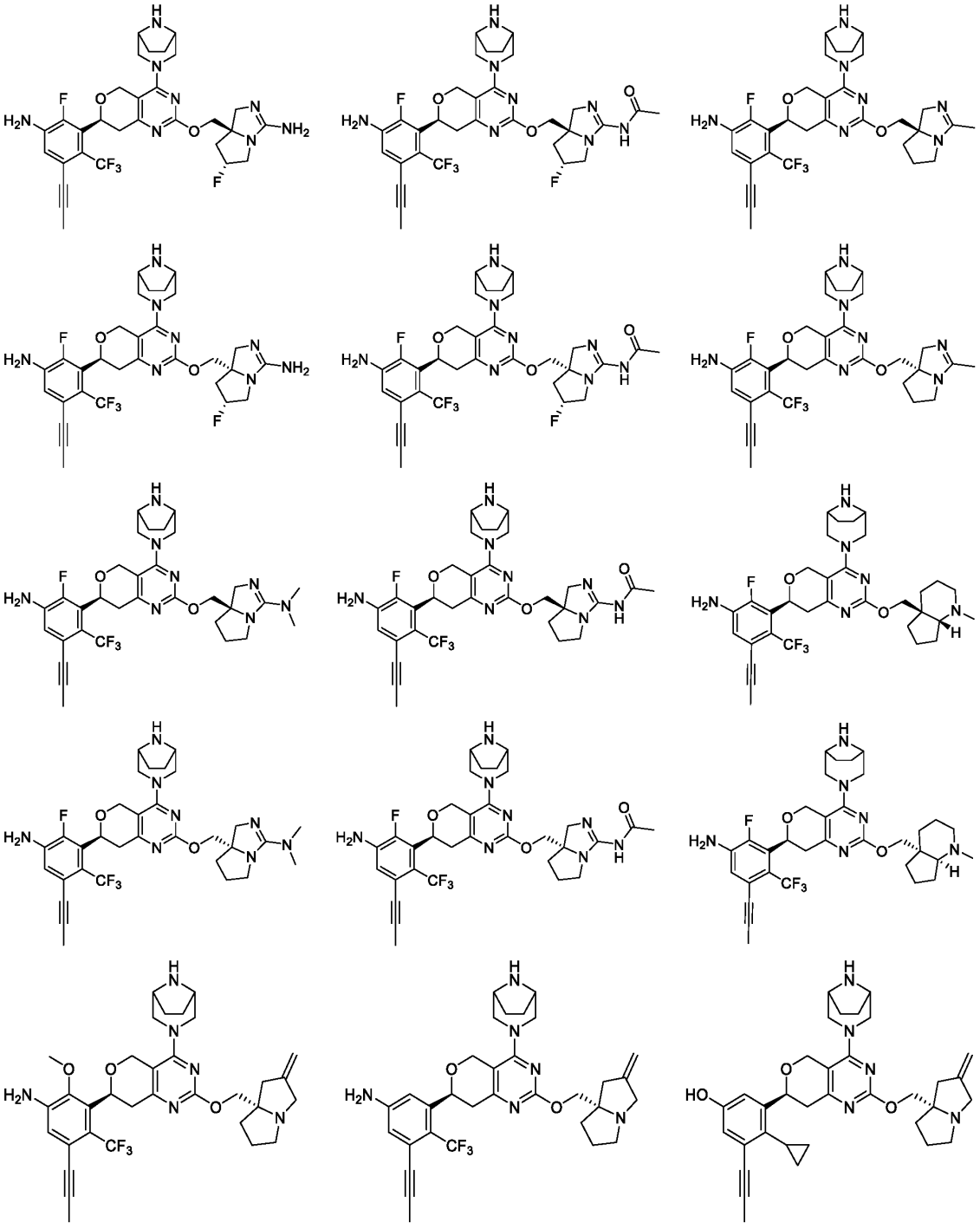
5 

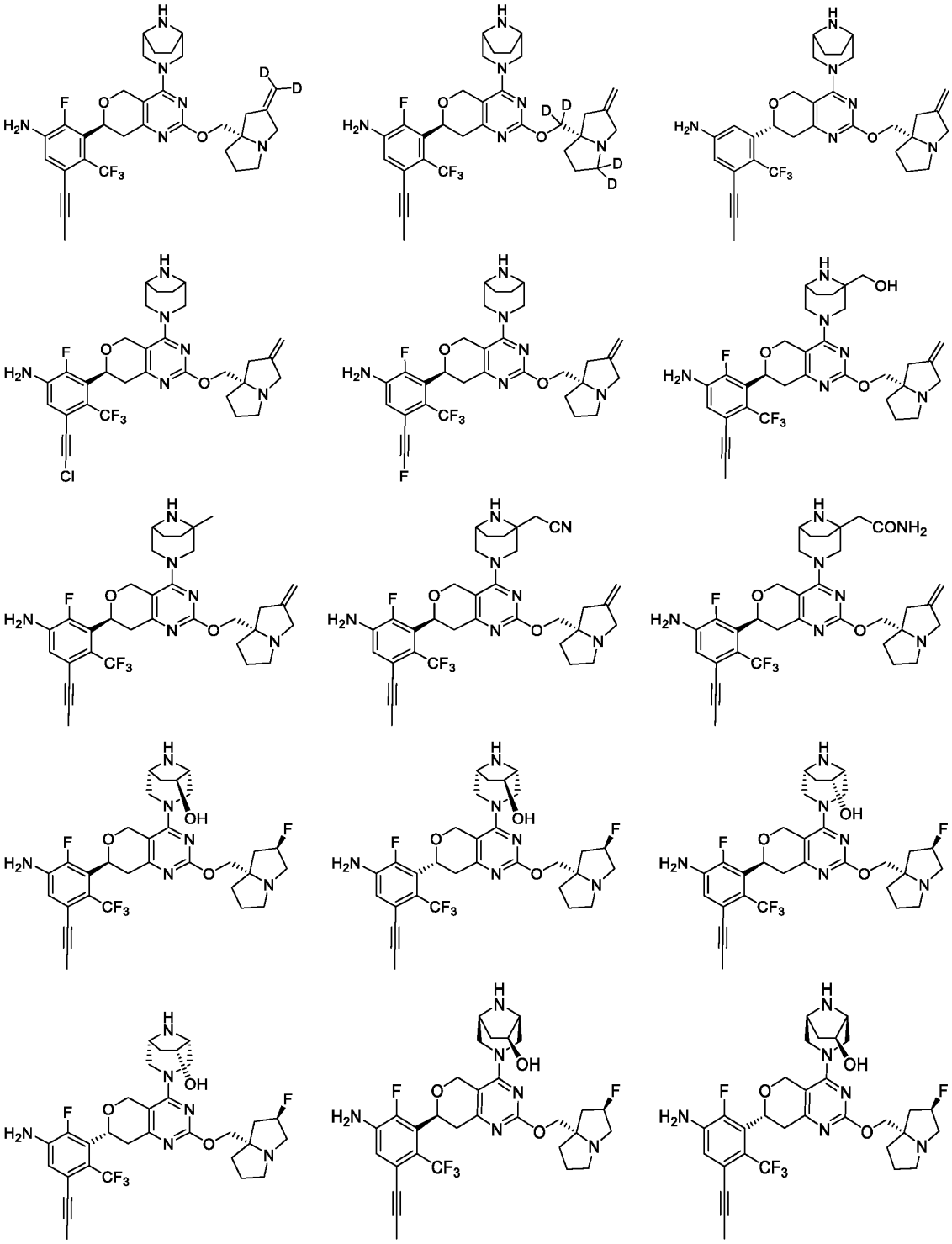
, a

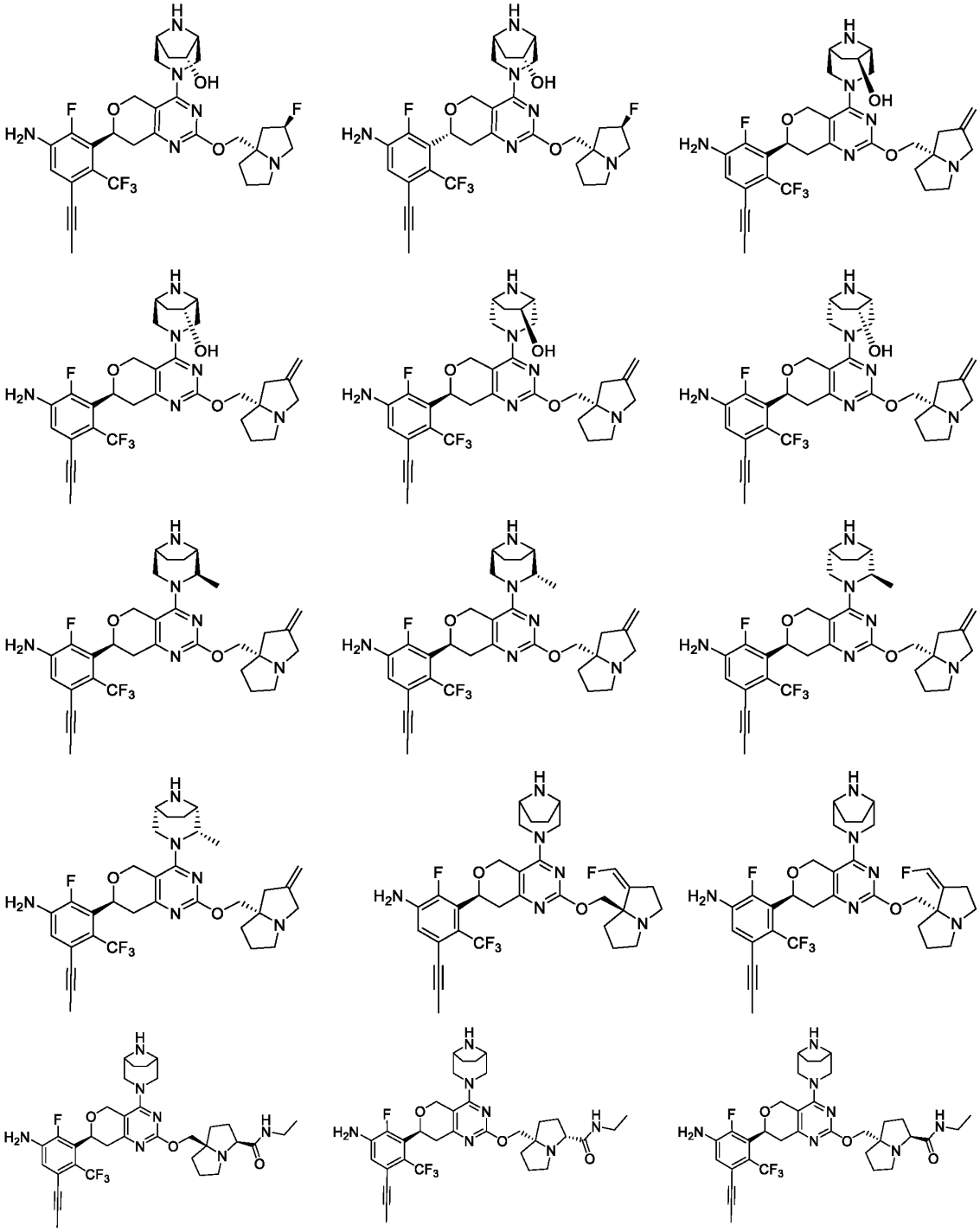
10 stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

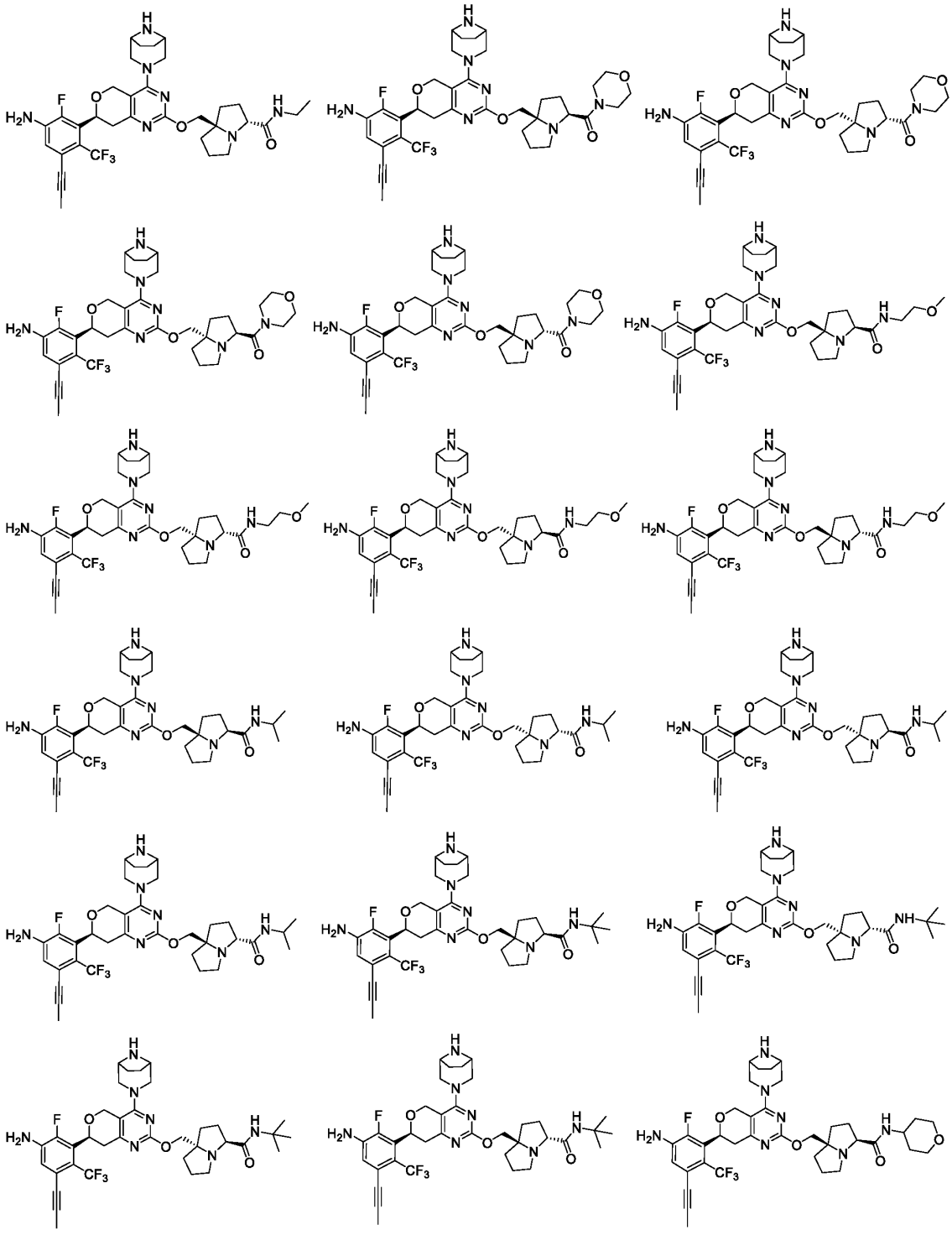
In some embodiments of the present disclosure, the compound is selected from:

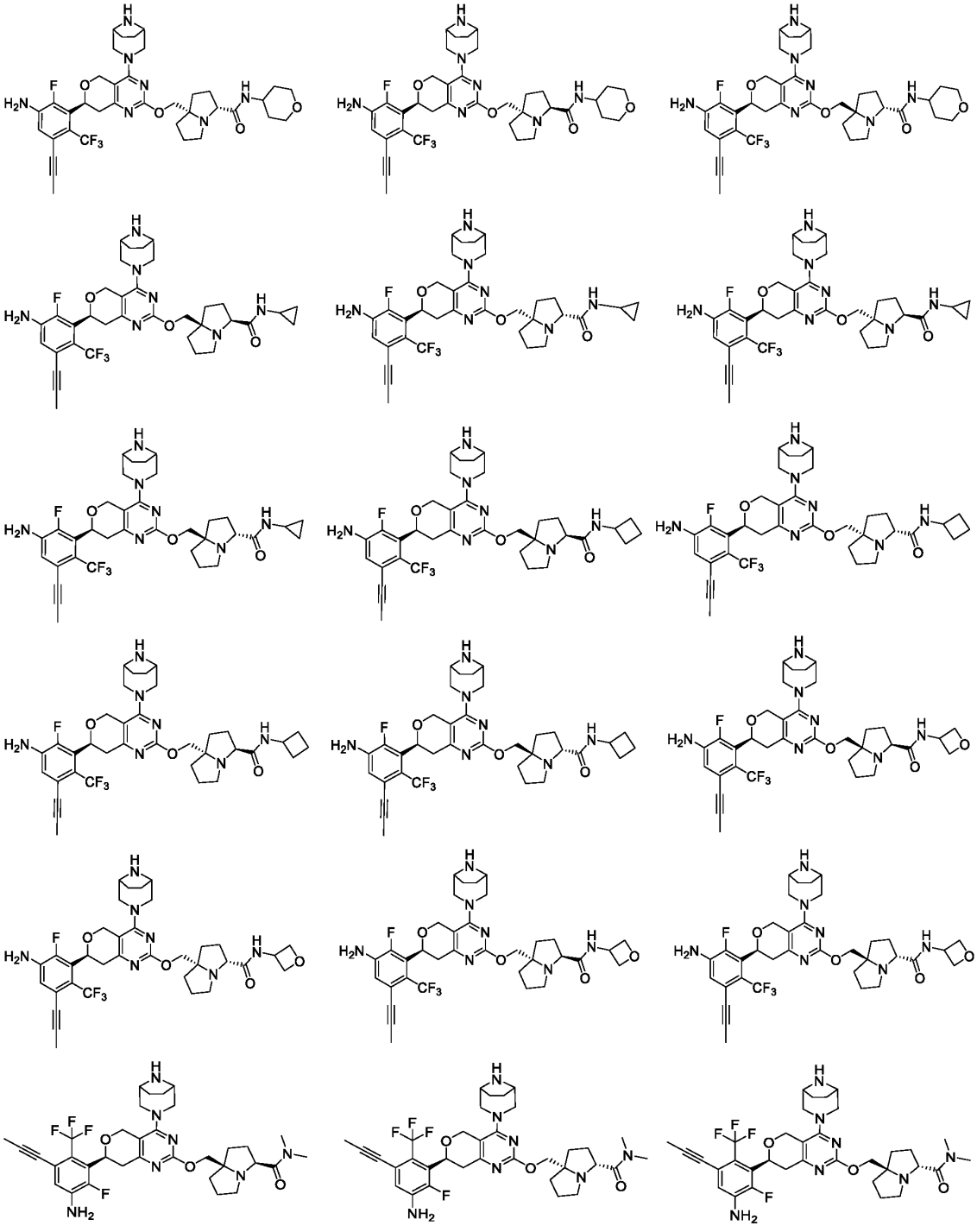


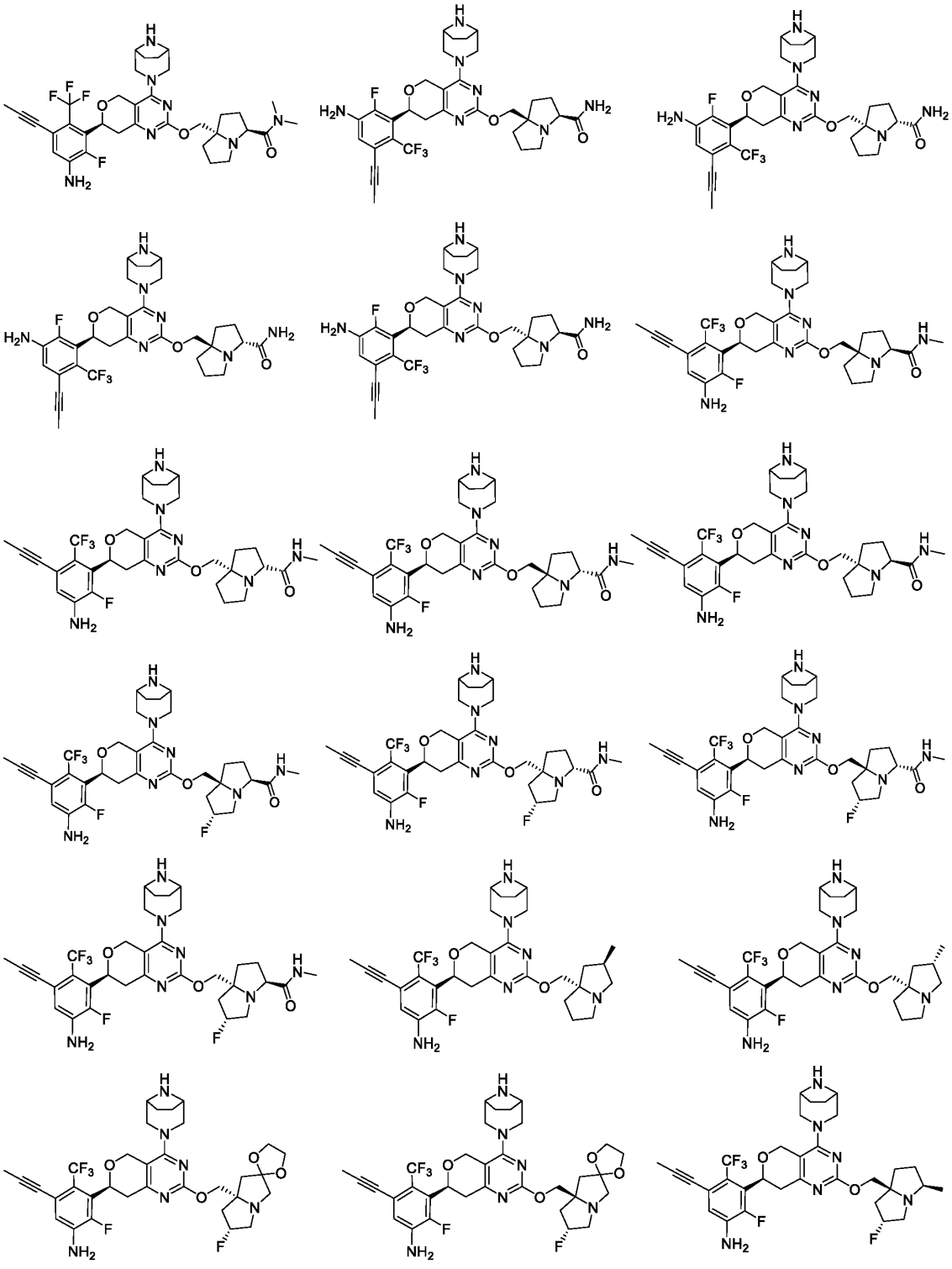


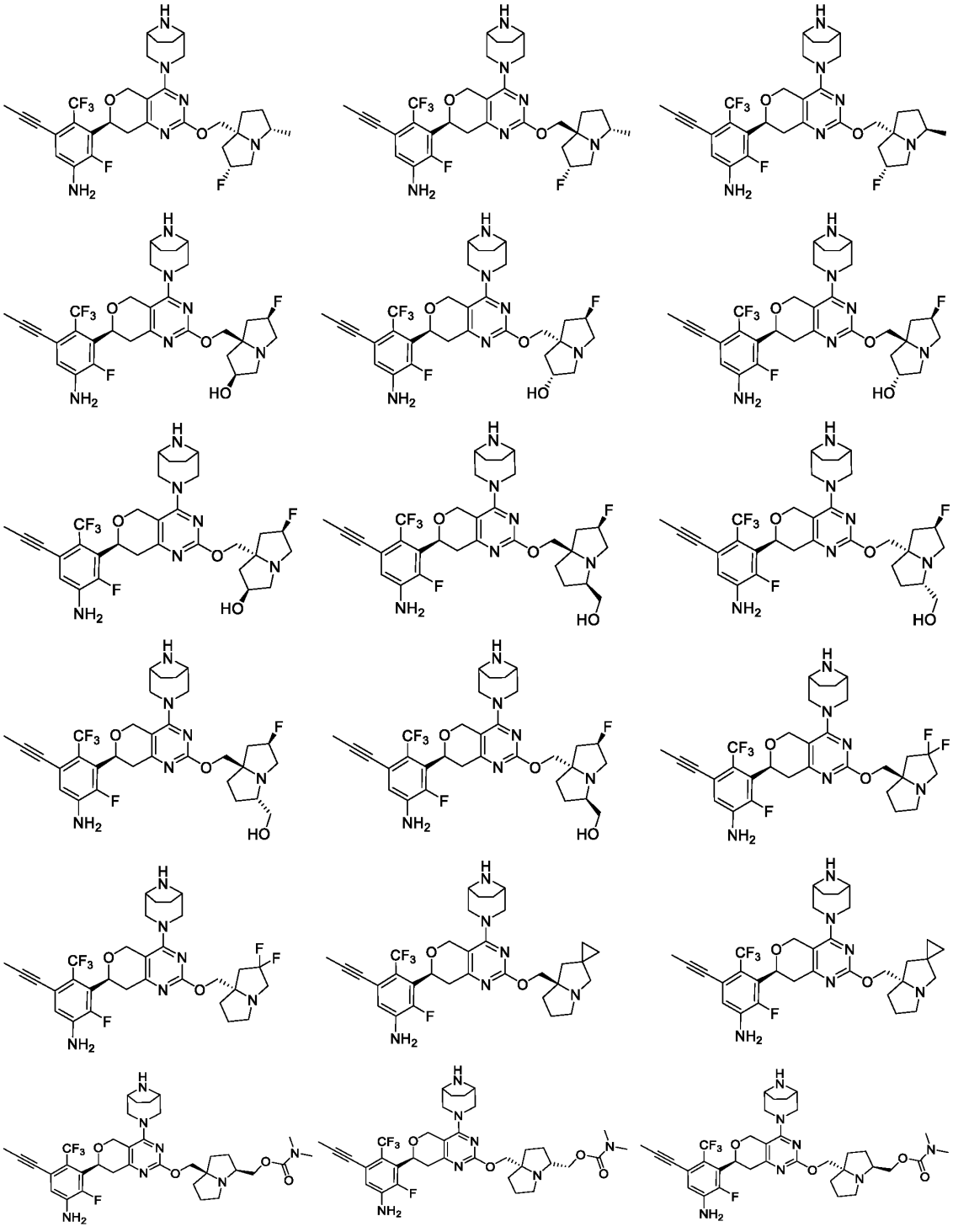


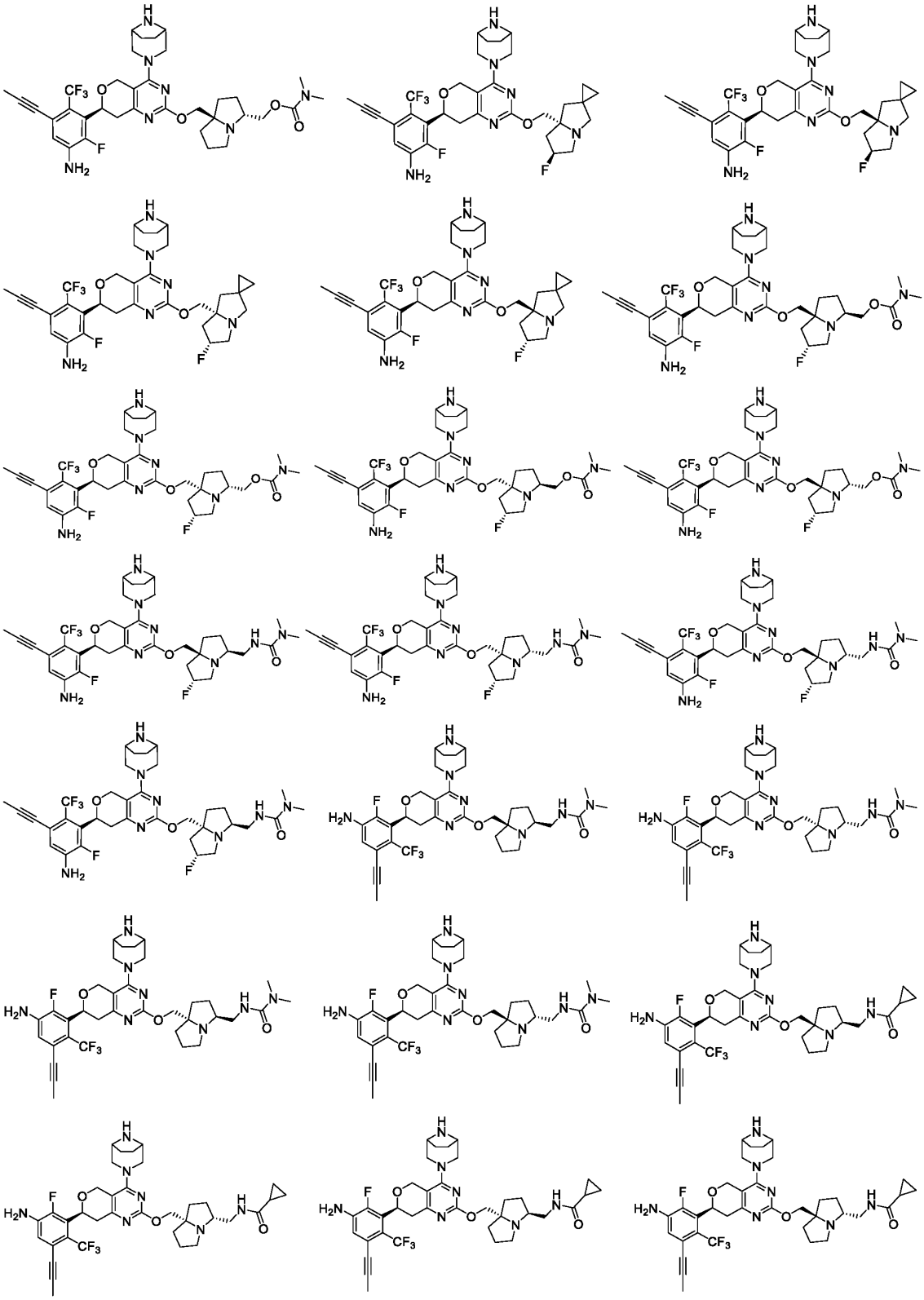


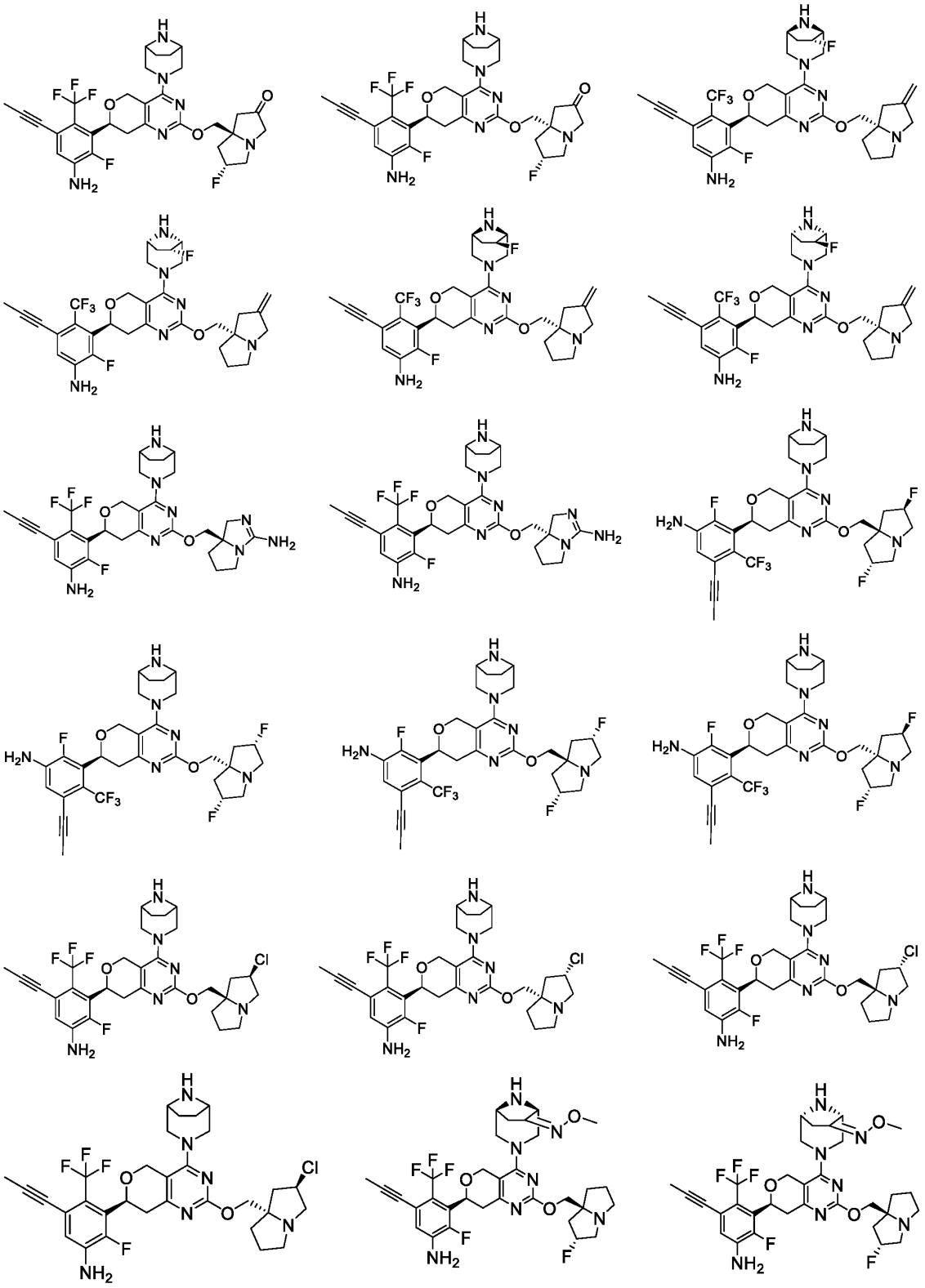


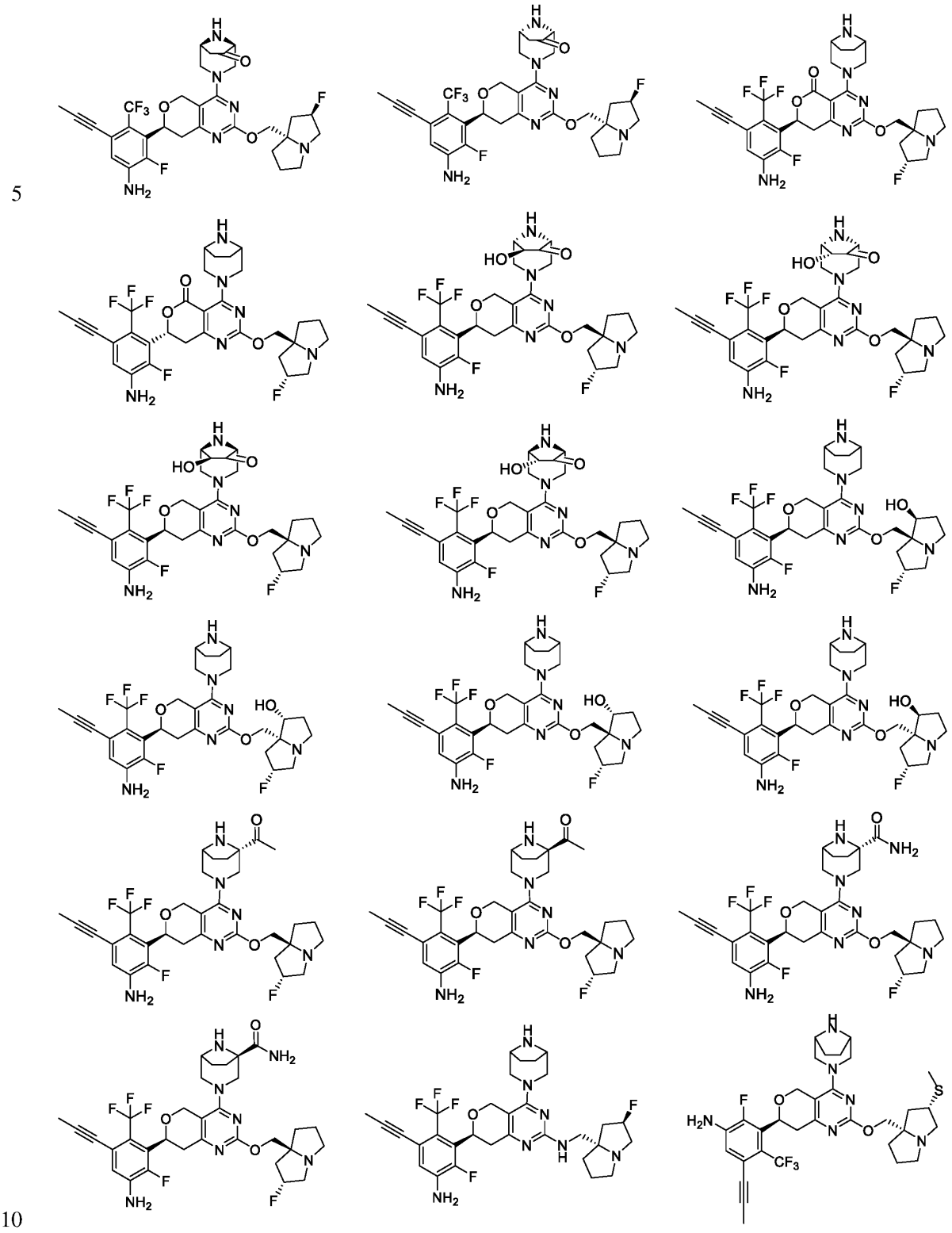


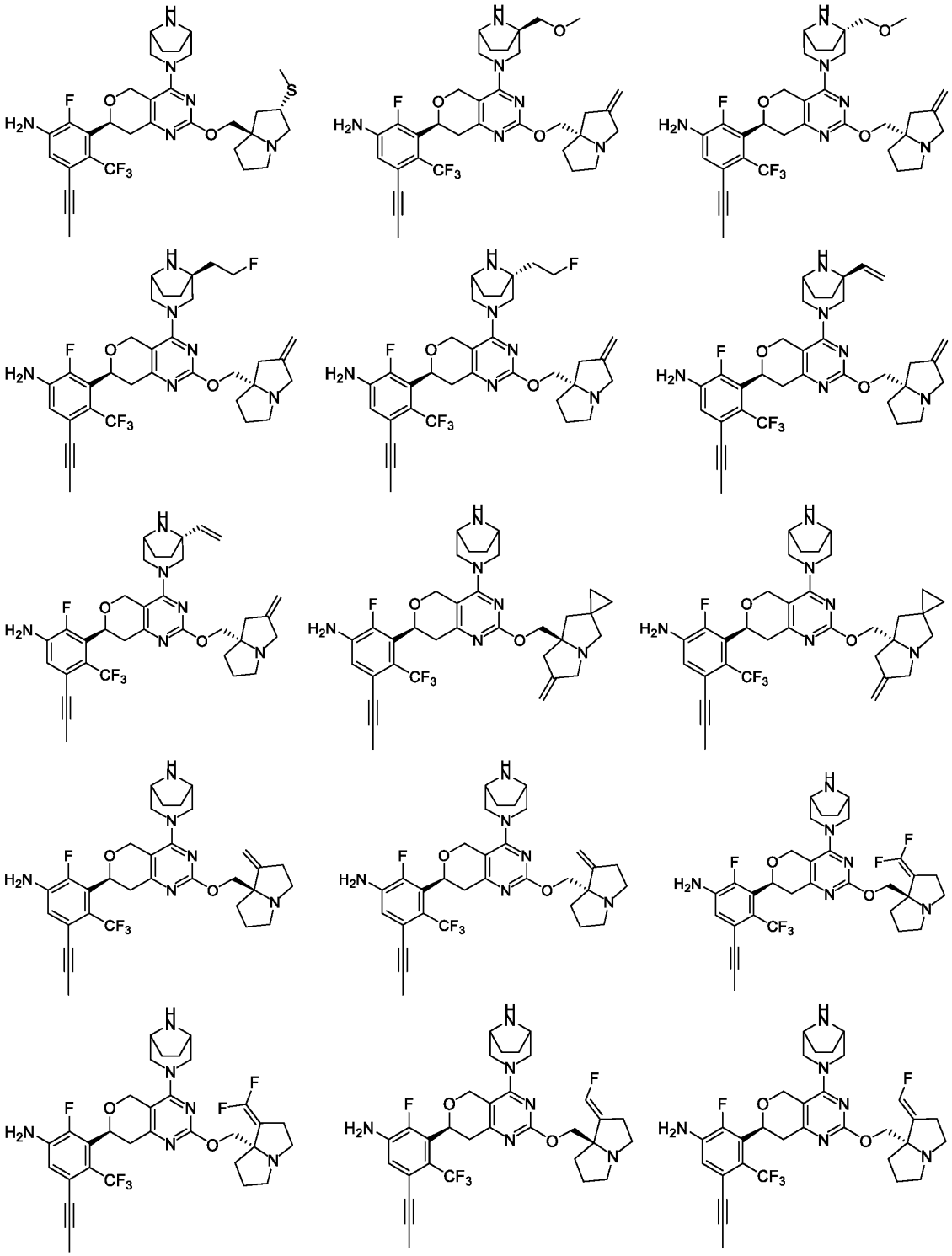


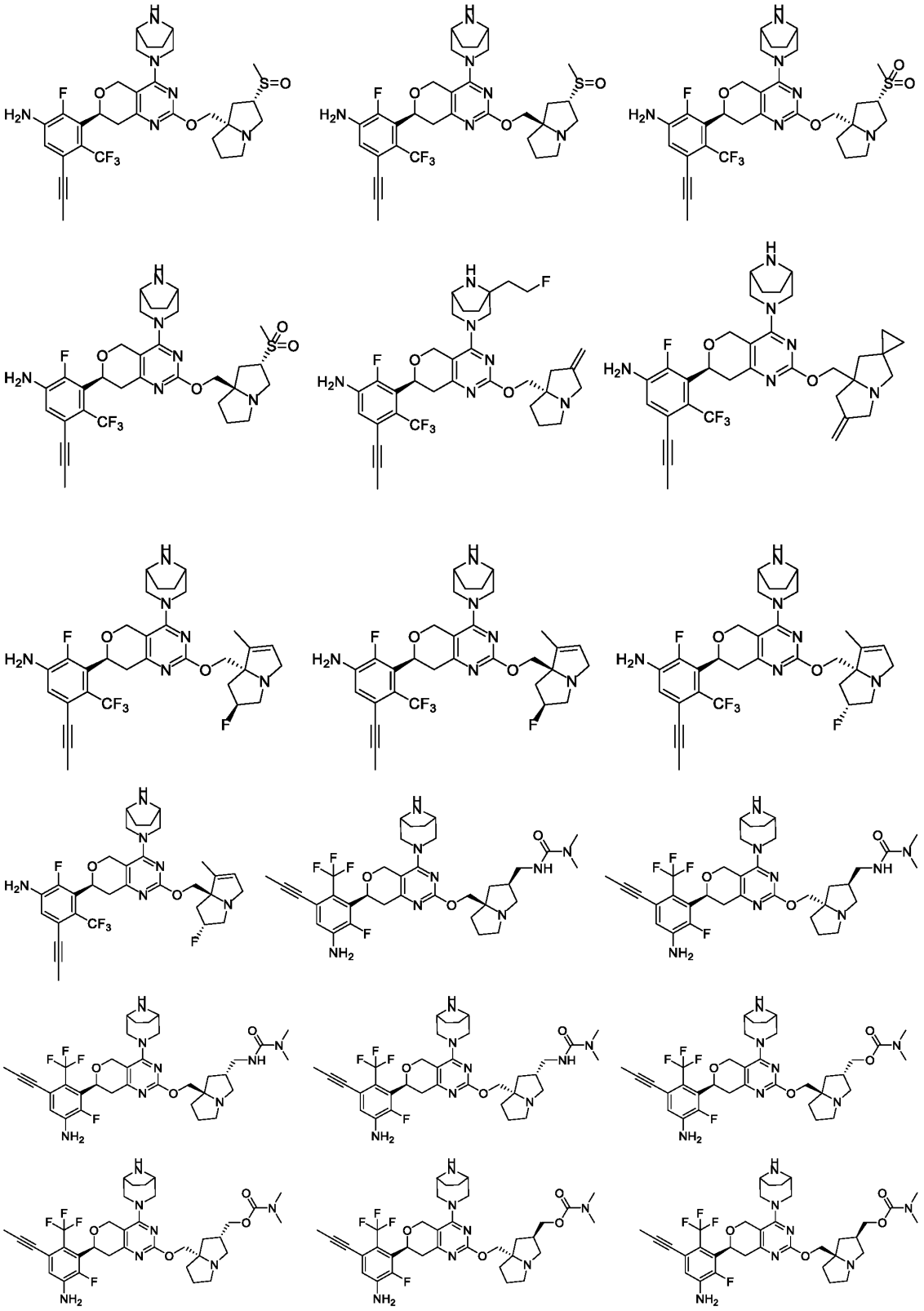


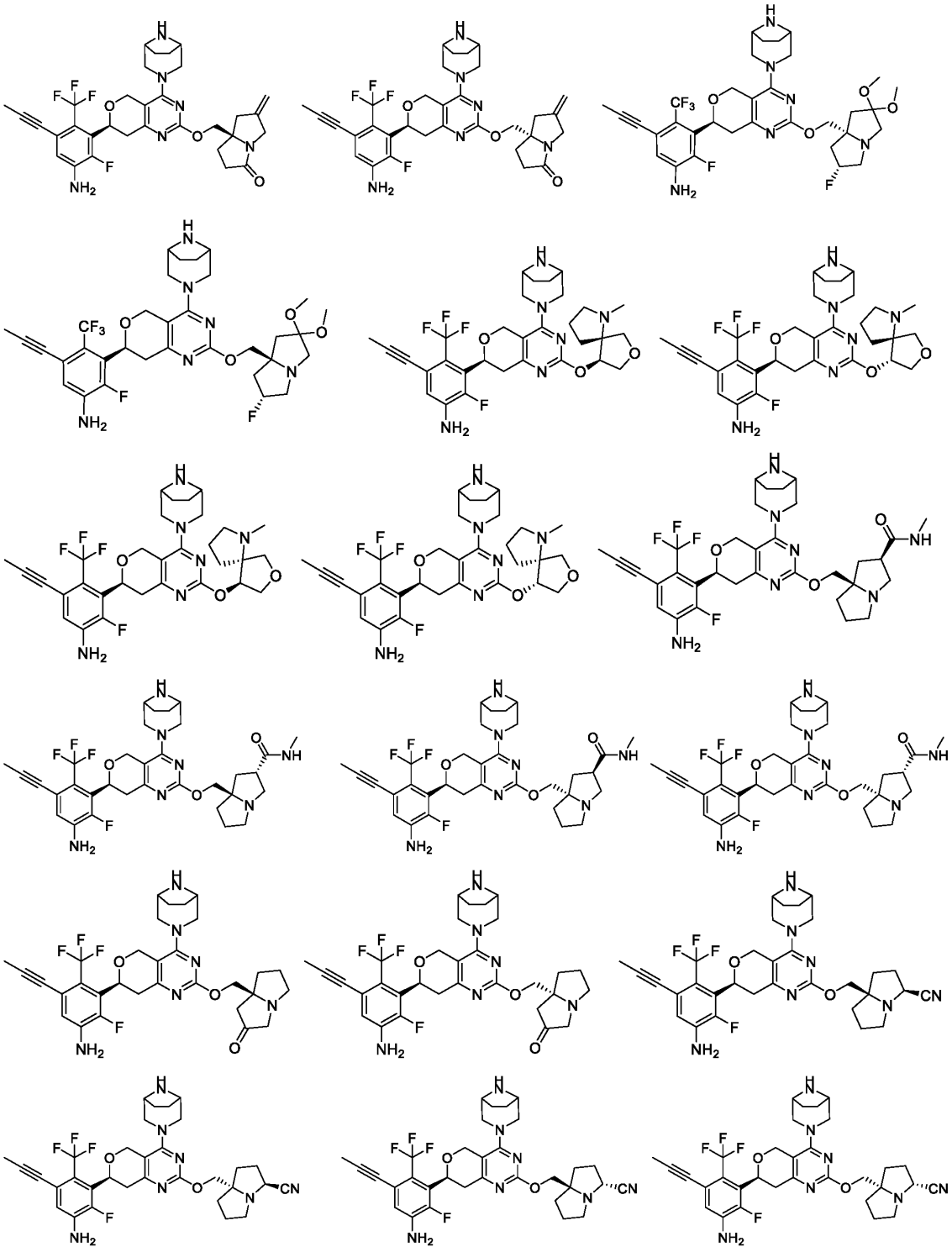












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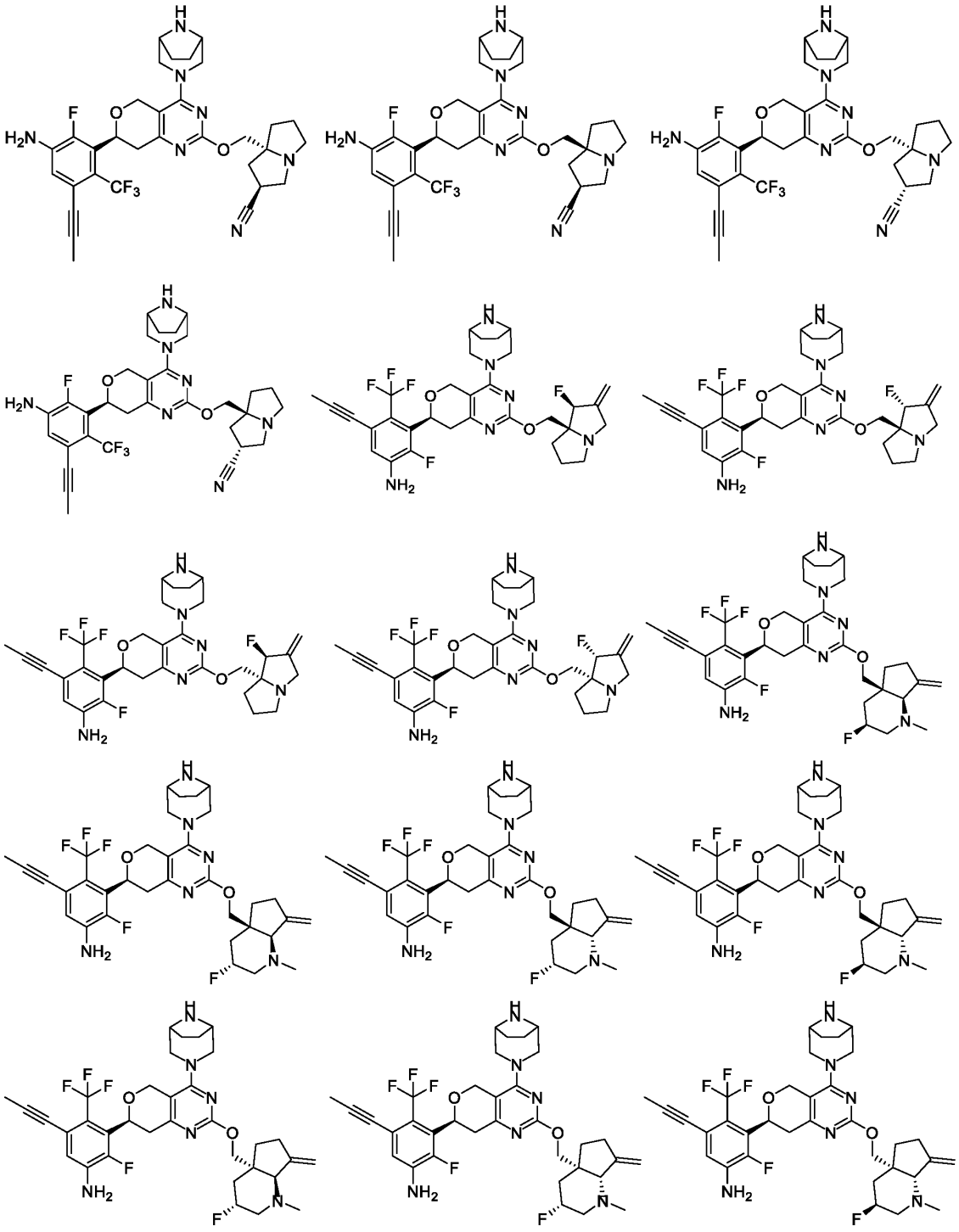
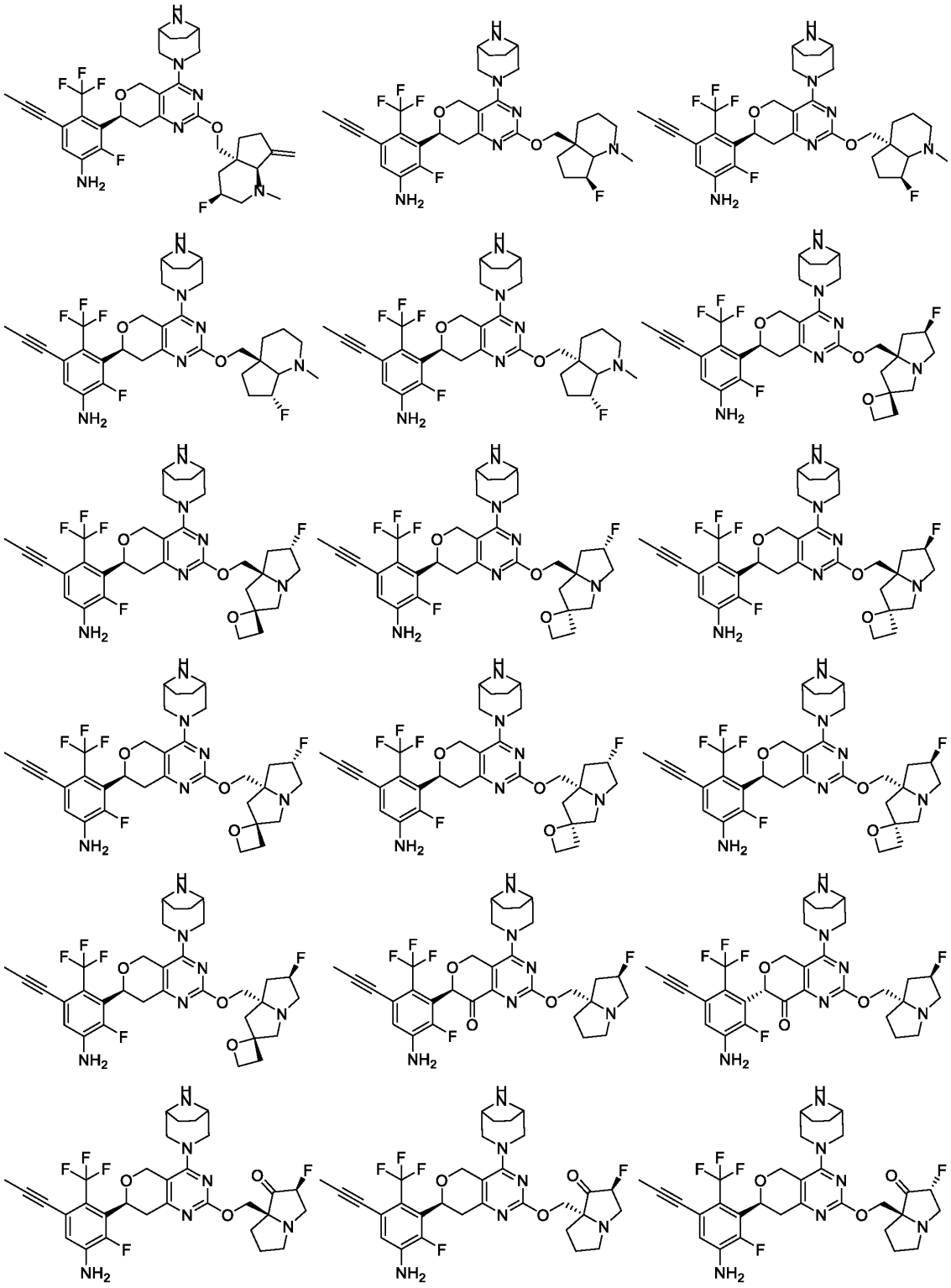
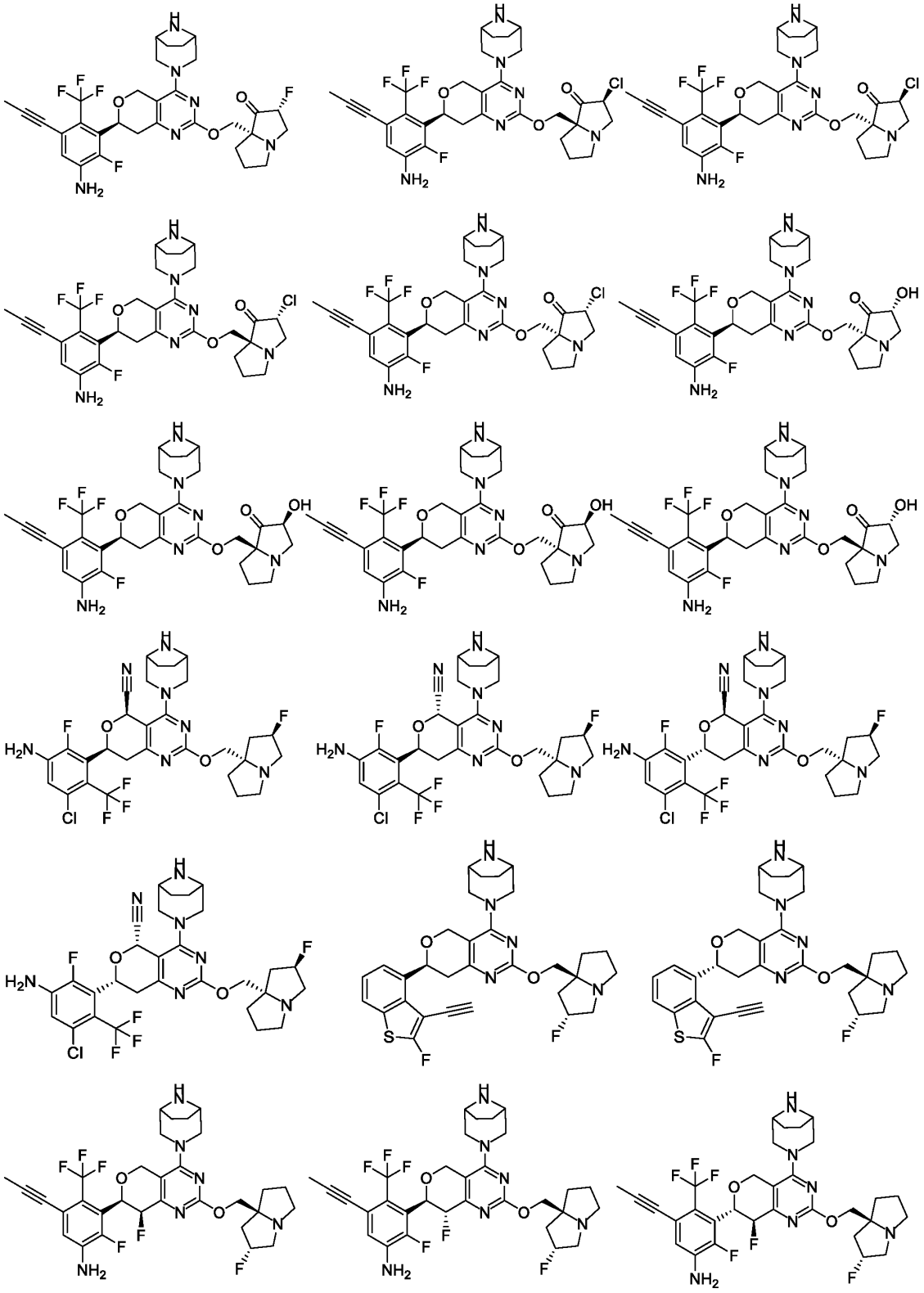
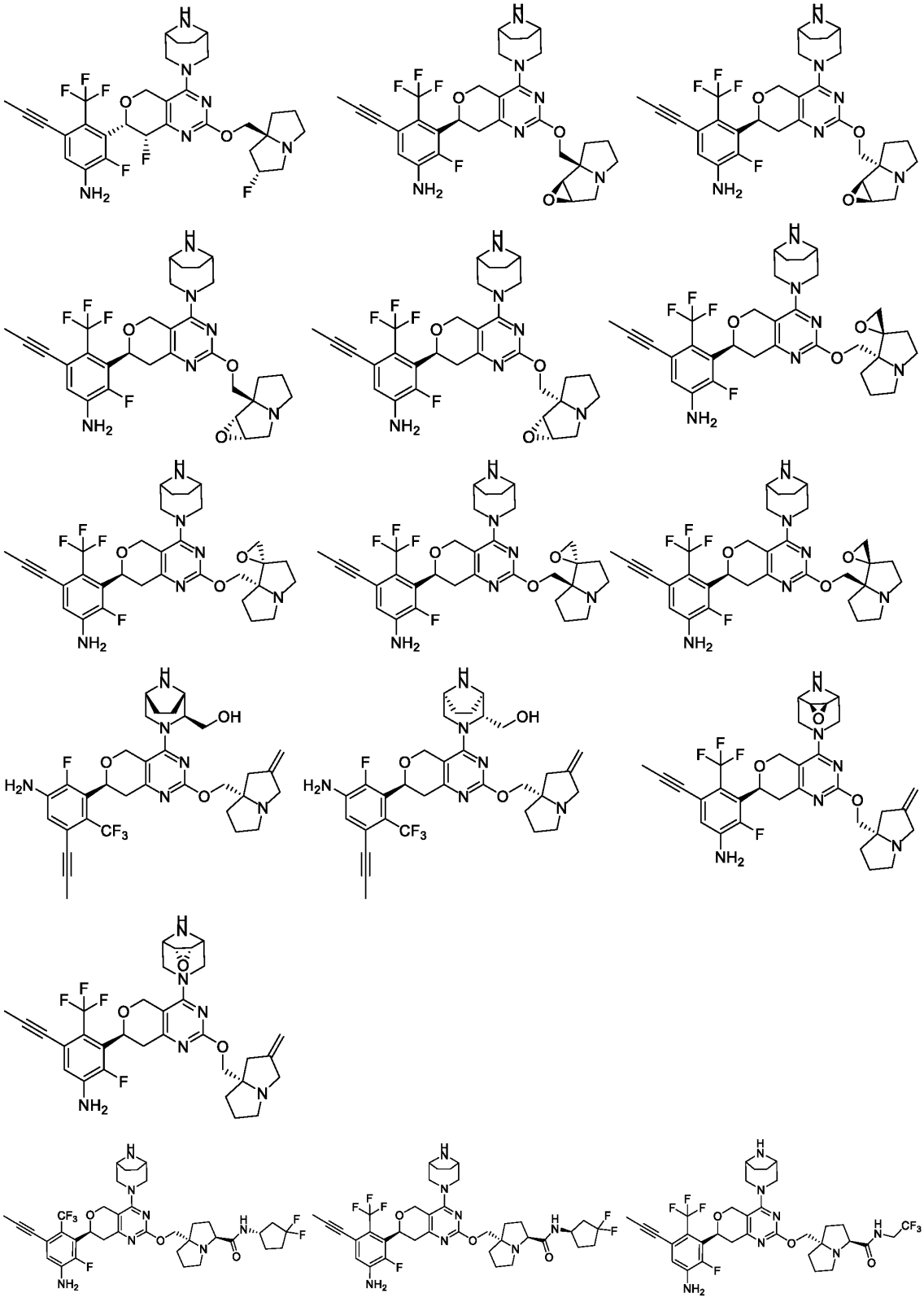
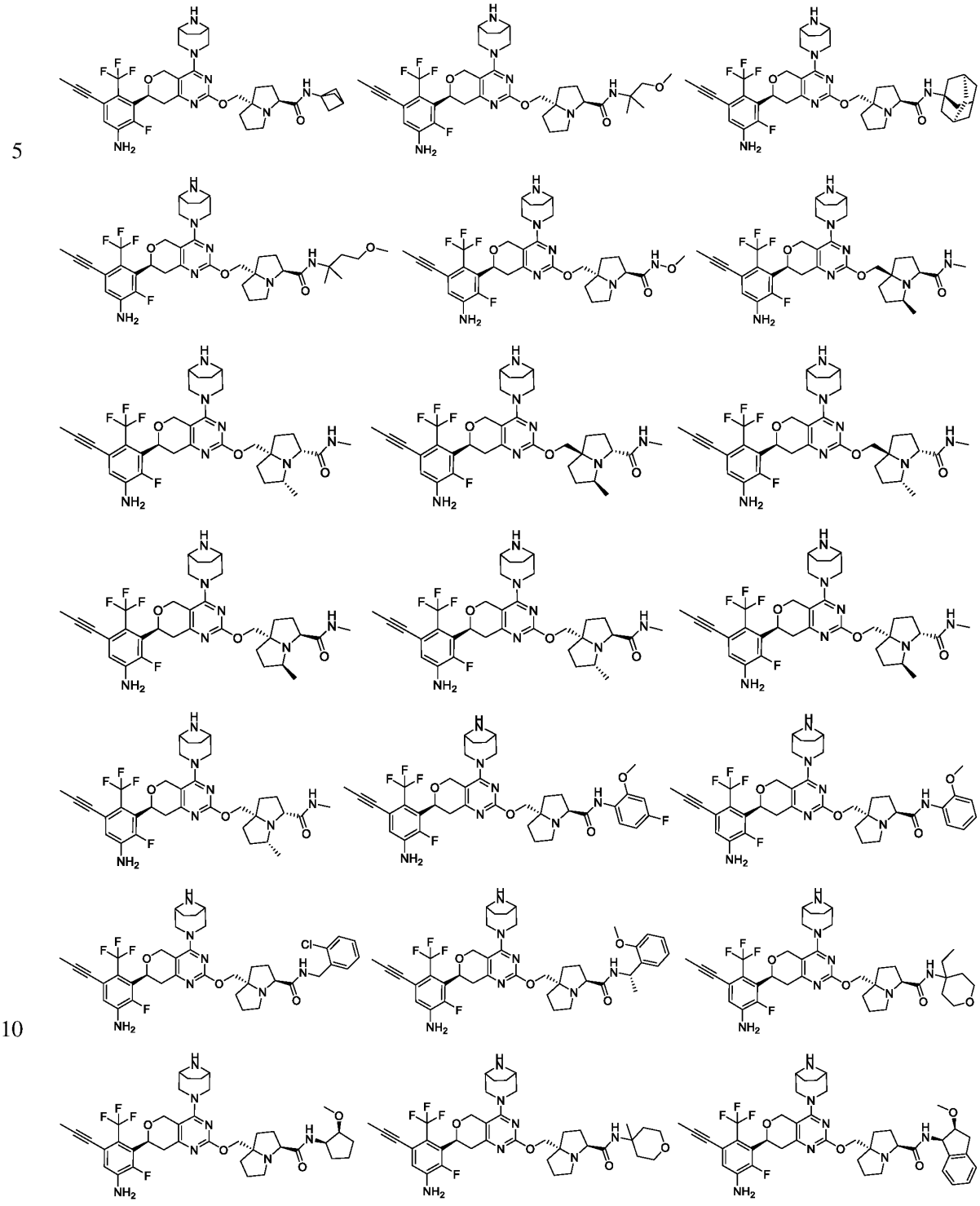
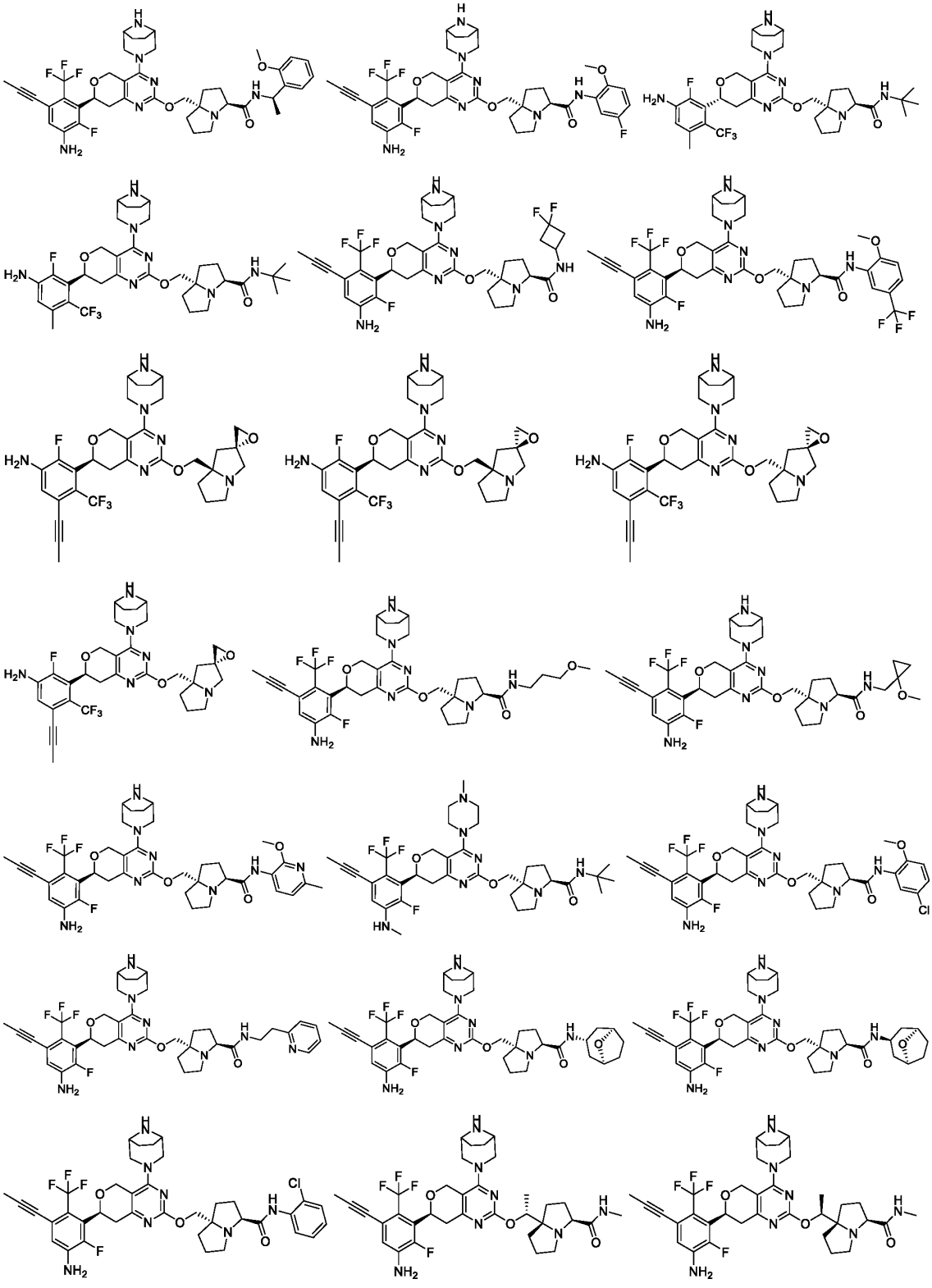


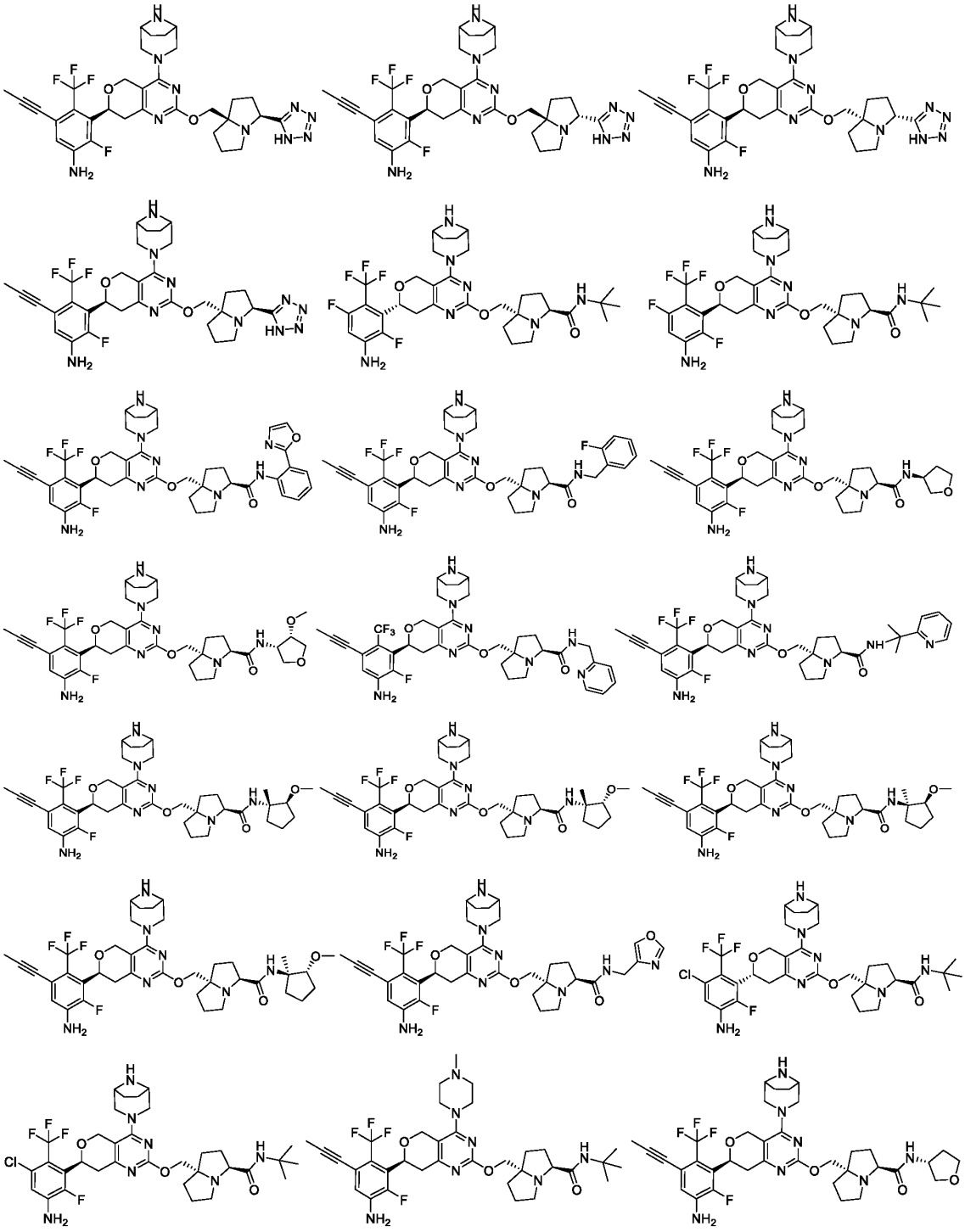


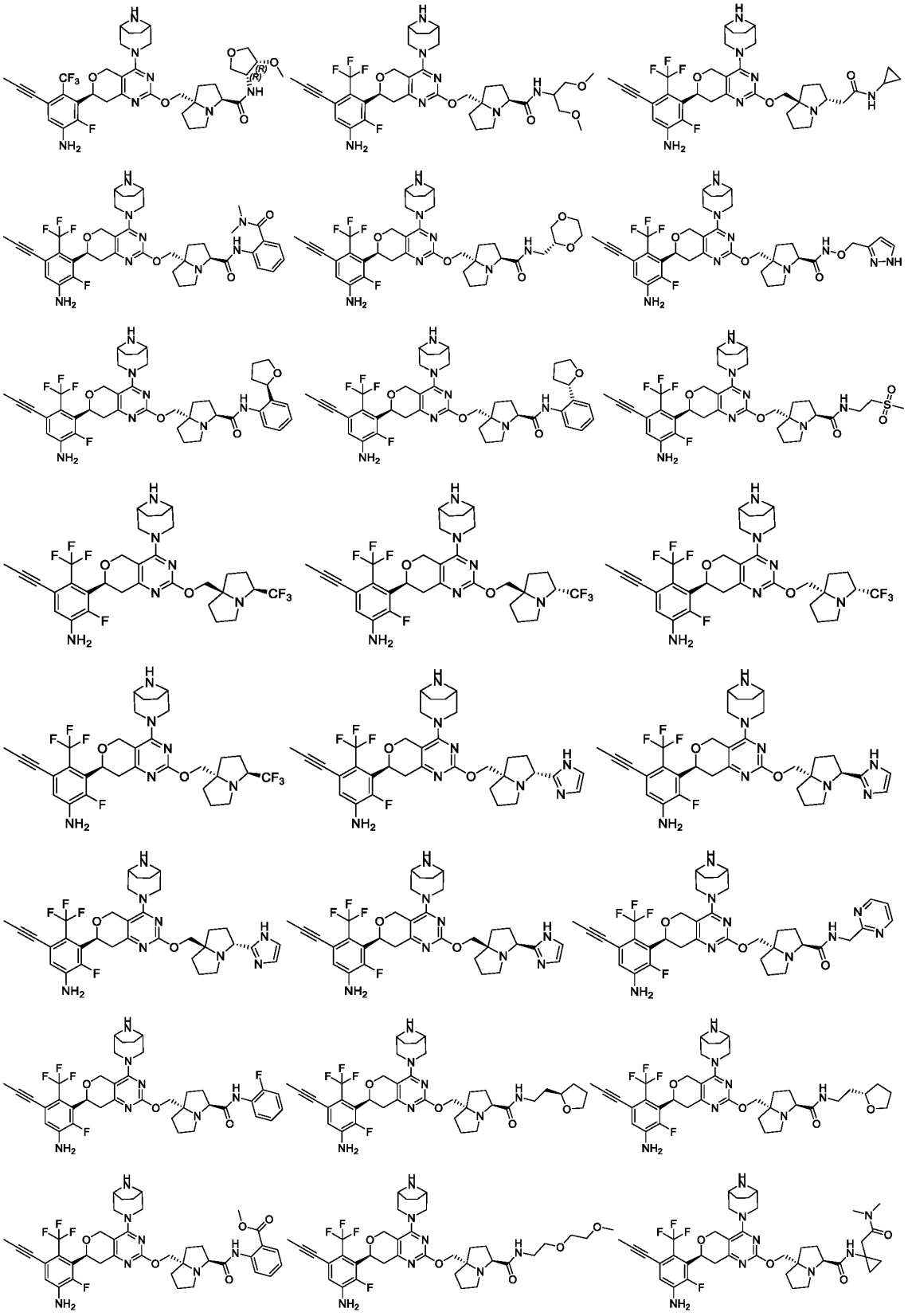


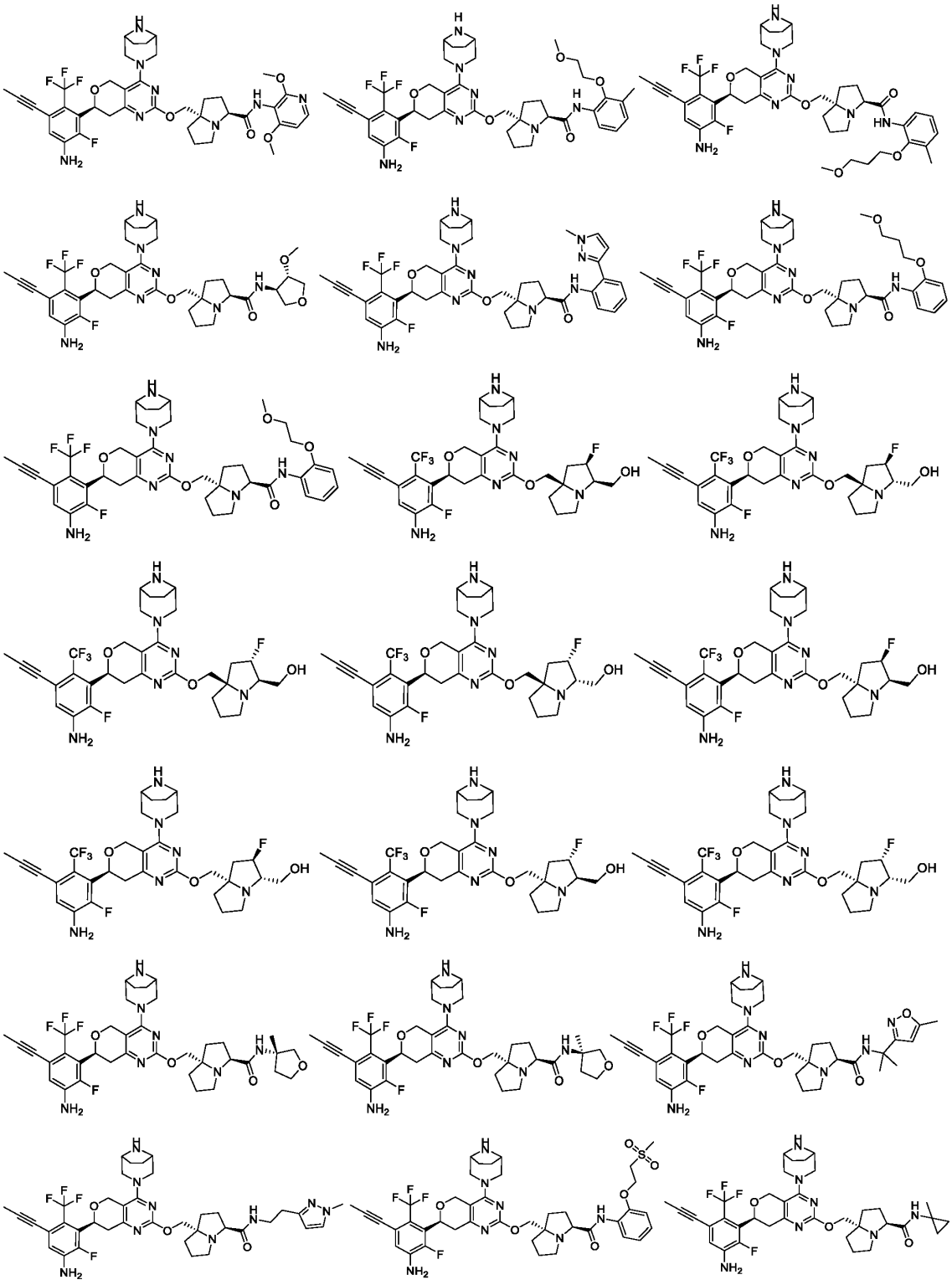


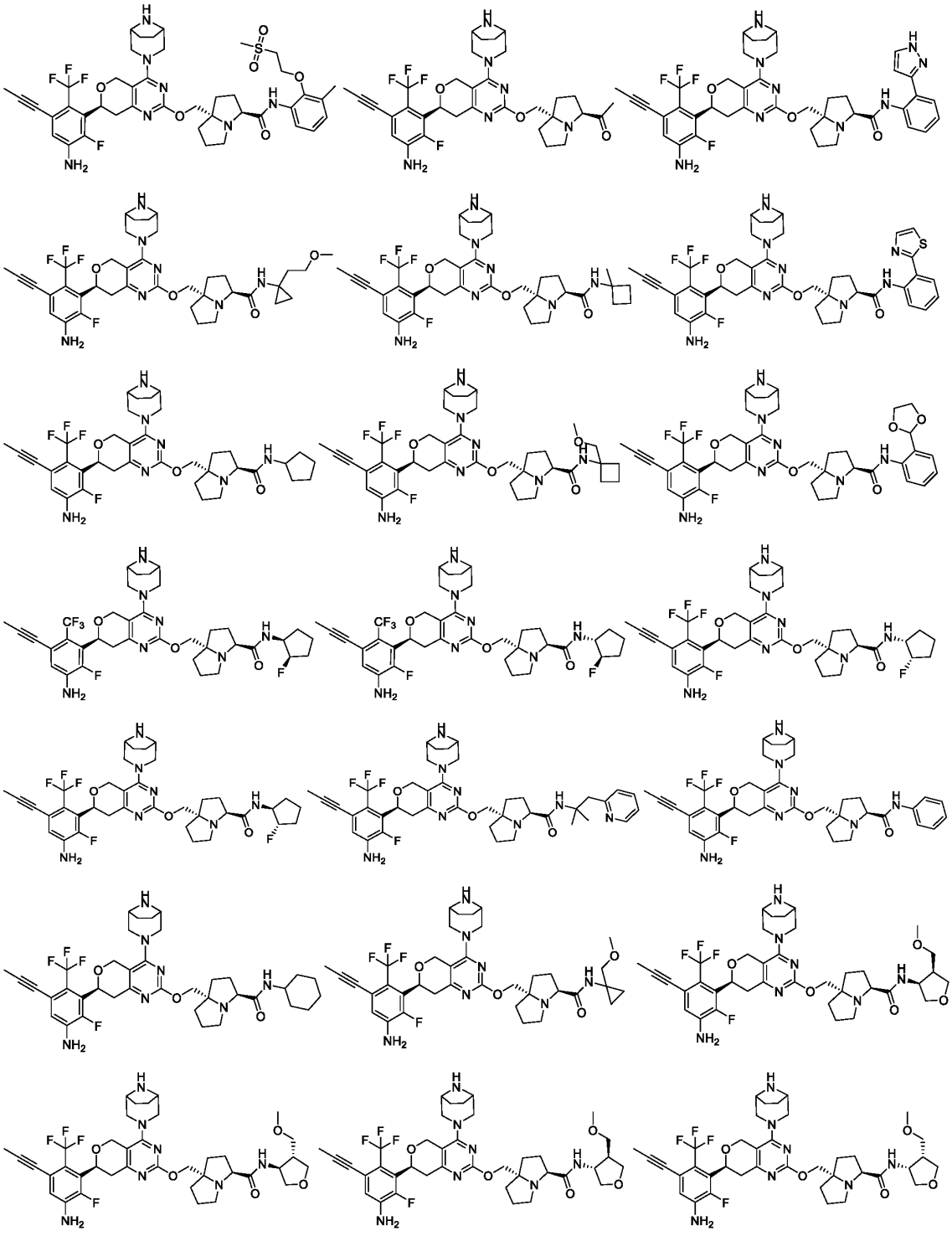


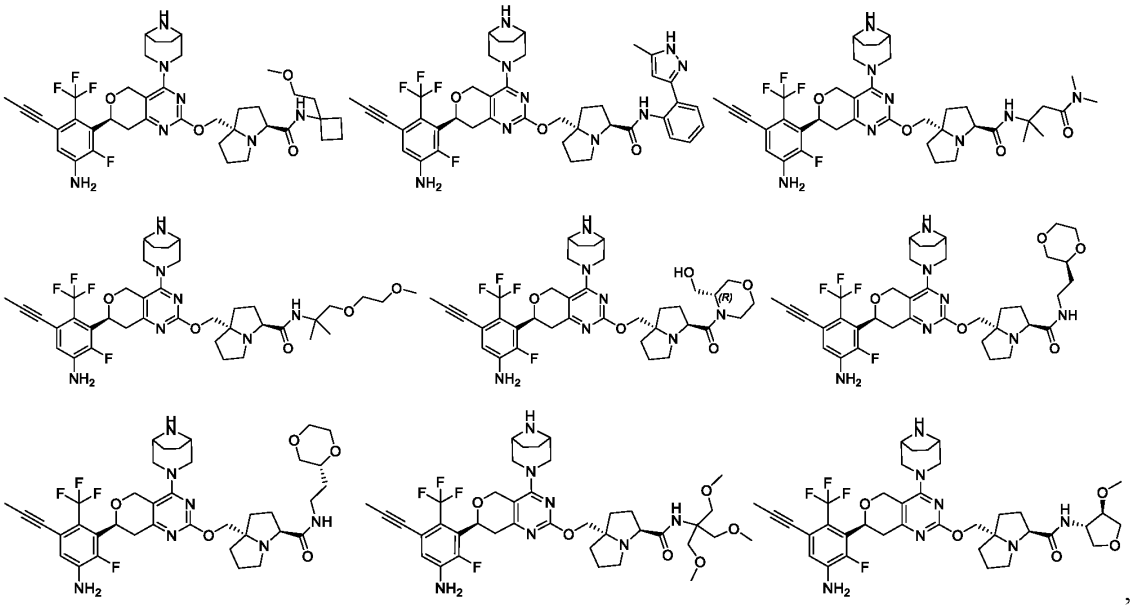






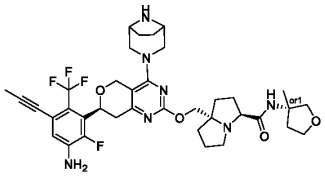
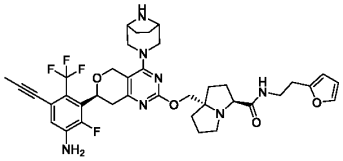
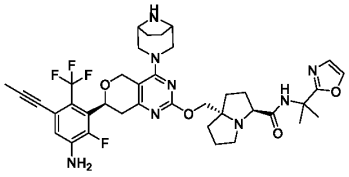
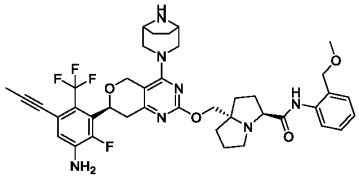
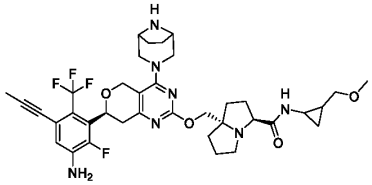
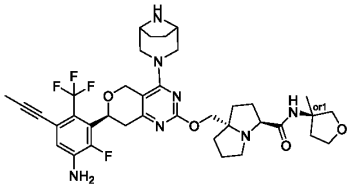
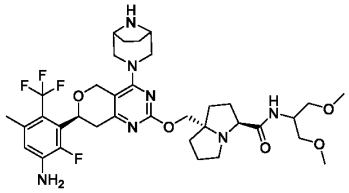
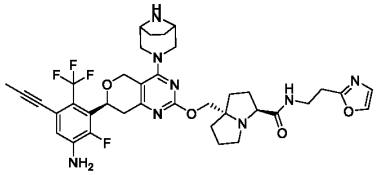
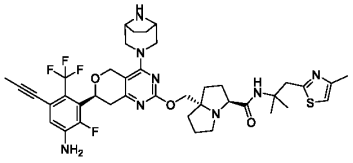


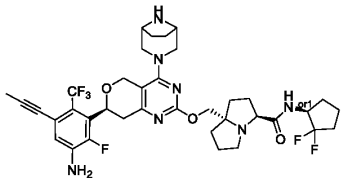
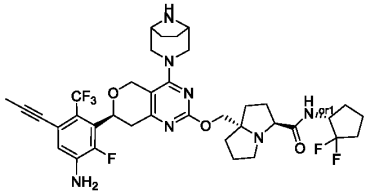
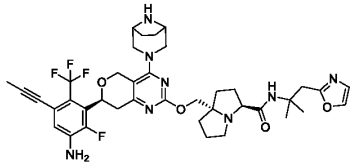
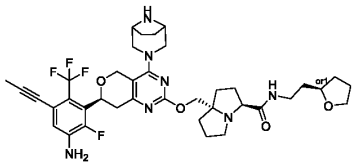
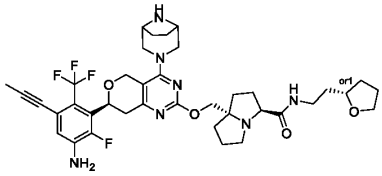
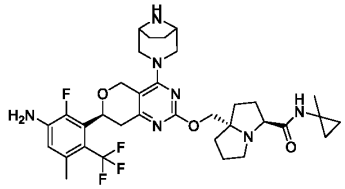
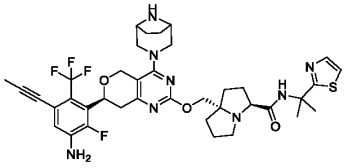
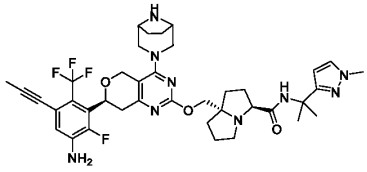
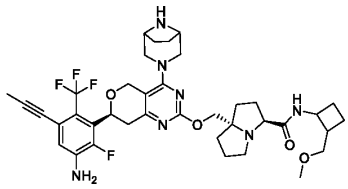
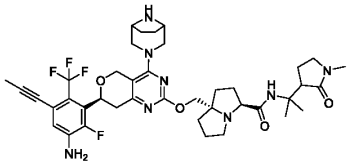
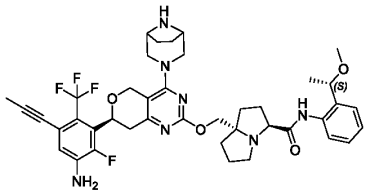
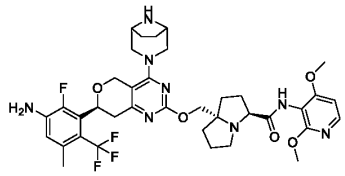
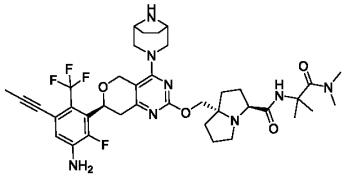
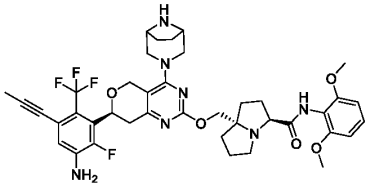
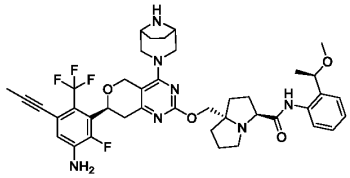
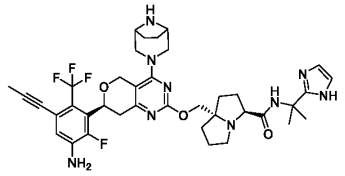
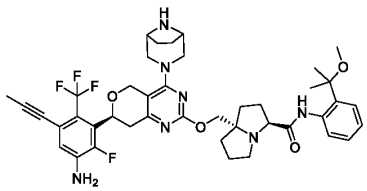
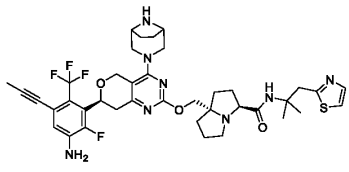


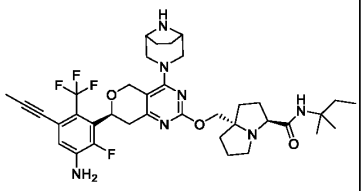
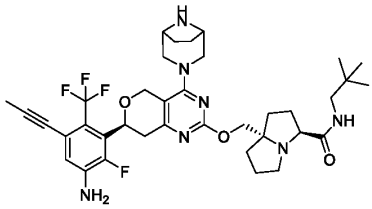
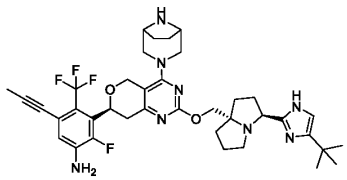
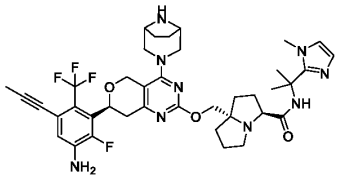
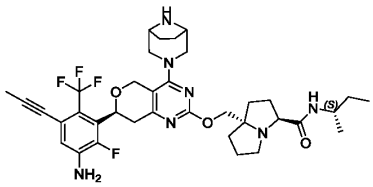
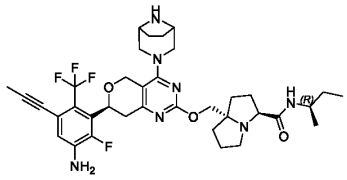
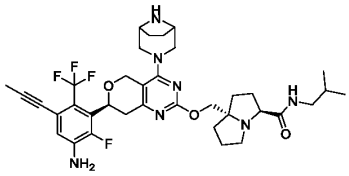
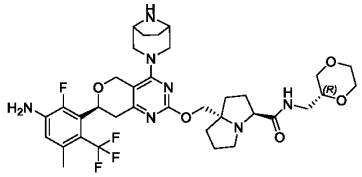
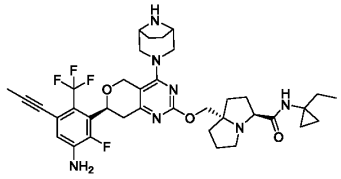
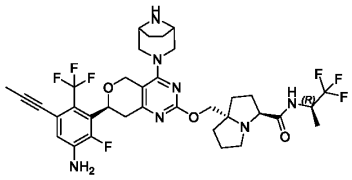
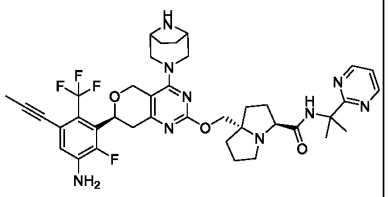
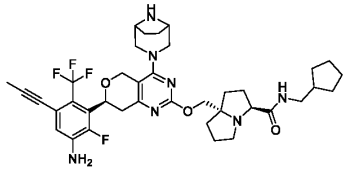
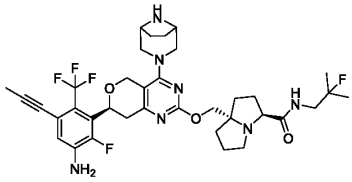
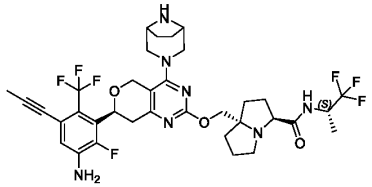
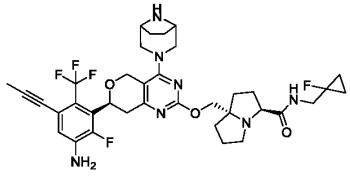
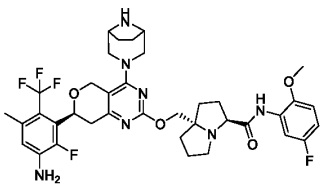
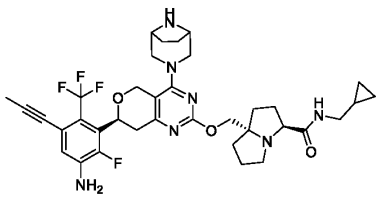
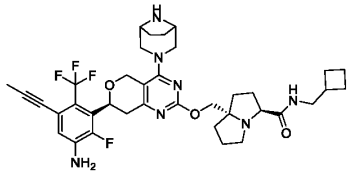


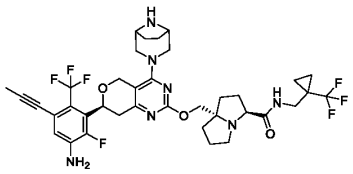
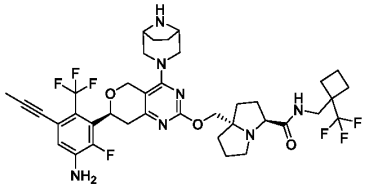
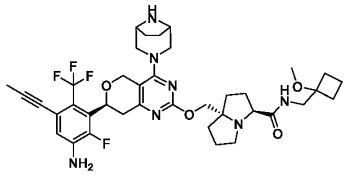
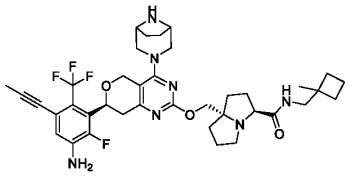
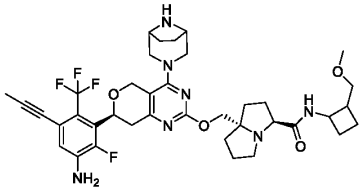
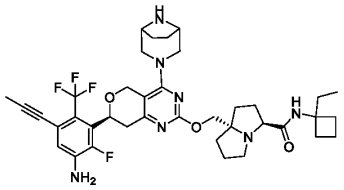
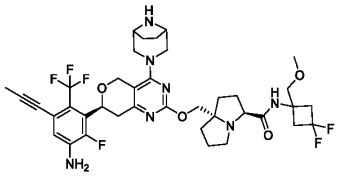
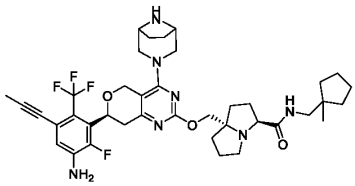
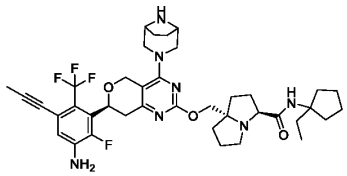
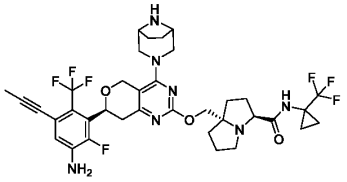
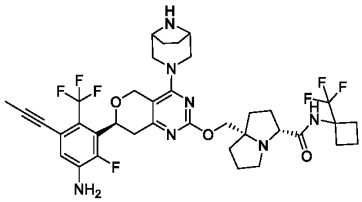
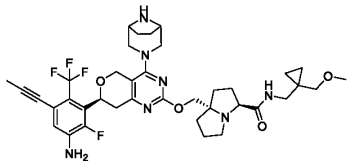
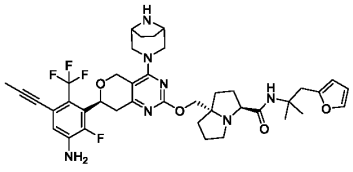
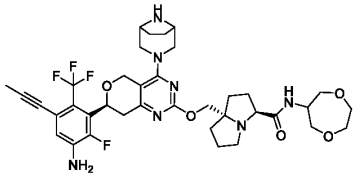
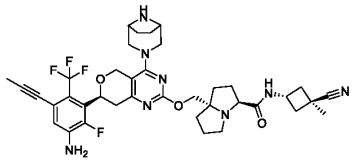
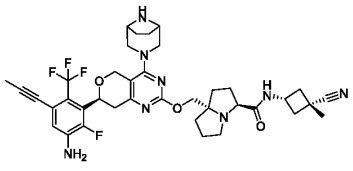
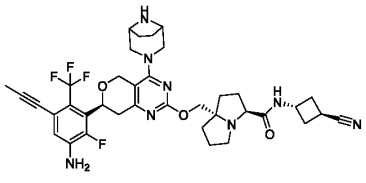
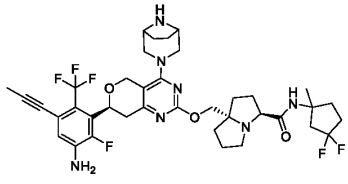
or a pharmaceutically acceptable salt thereof.

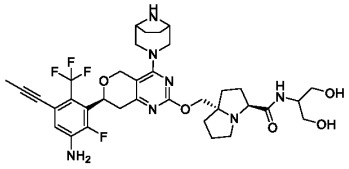
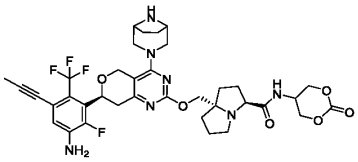
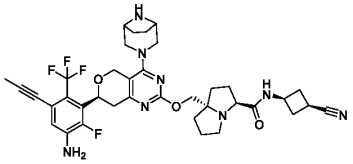
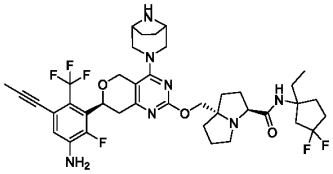
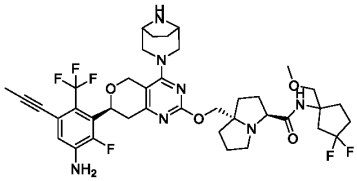
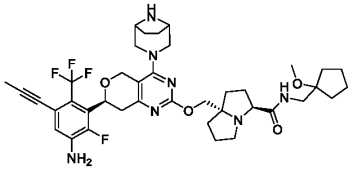
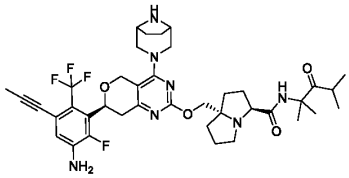
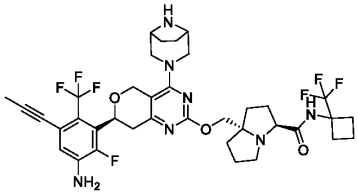
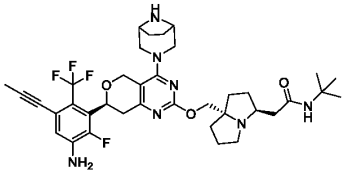
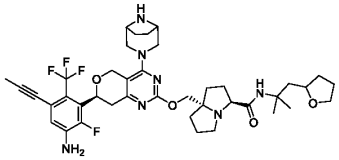
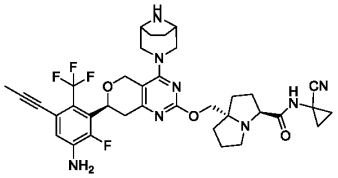
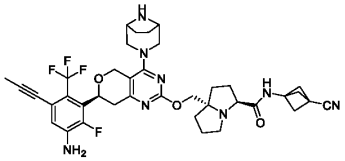
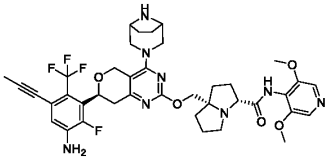
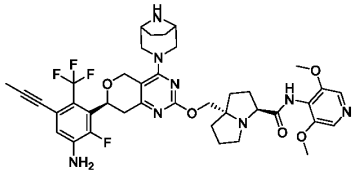
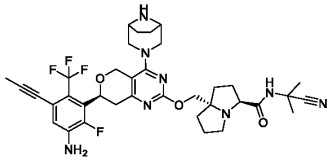
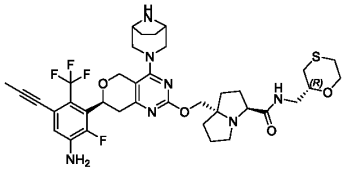
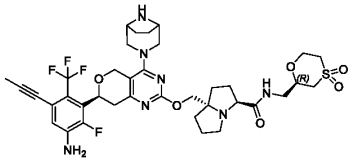
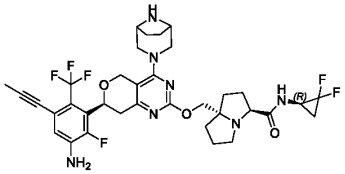
Table 5

Example S1 	Example S2 	Example S3 
Example S4 	Example S5 (mix of 4 isomers) 	Example S6 
Example S7 	Example S8 	Example S9 

Example S10 	Example S11 	Example S12 
Example S13 	Example S14 	Example S15 
Example S16 	Example S17 	Example S18A/S18B 
Example S19A/S19B 	Example S20 	Example S21 
Example S22 	Example S23 	Example S24 
Example S25 	Example S26 	Example S27 

Example S28 	Example S29 	Example S30 
Example S31 	Example S32 	Example S33 
Example S34 	Example S35 	Example S36 
Example S37 	Example S38 	Example S39 
Example S40 	Example S41 	Example S42 
Example S43 	Example S44 	Example S45 

Example S46 	Example S47 	Example S48 
Example S49 	Example S50A/S50B 	Example S51 
Example S52 	Example S53 	Example S54 
Example S55 	Example S56 	Example S57 
Example S58 	Example S59 	Example S60 
Example S61 	Example S62 	Example S63A/S63B 

Example S64 	Example S65 	Example S66 
Example S67A/S67B 	Example S68A/S68B 	Example S69 
Example S70 	Example S71 	Example S72 
Example S73A/S73B 	Example S74 	Example S75 
Example S76 	Example S77 	Example S78 
Example S79 	Example S80 	Example S81 

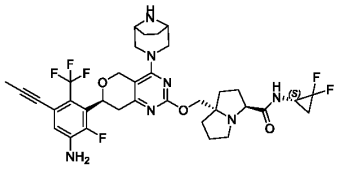
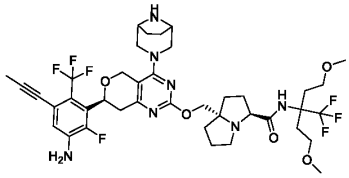
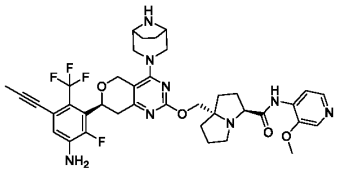
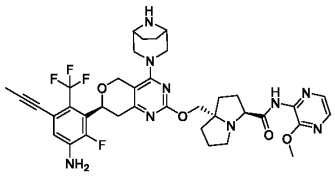
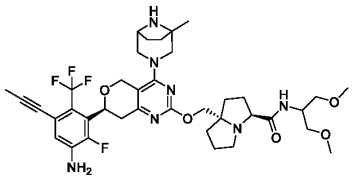
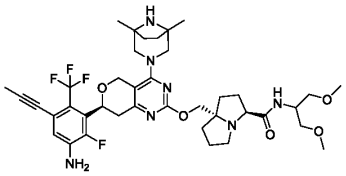
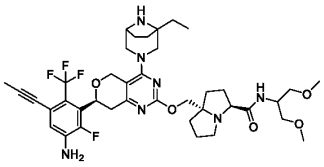
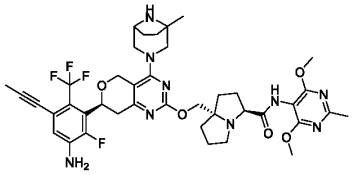
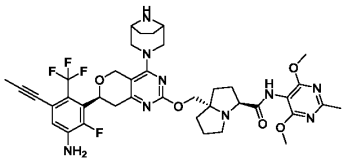
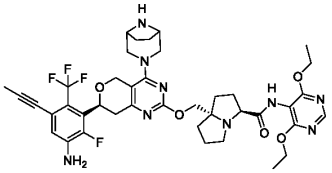
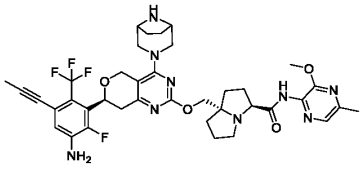
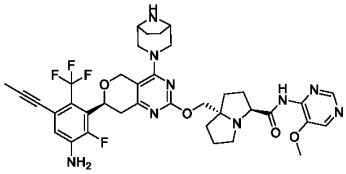
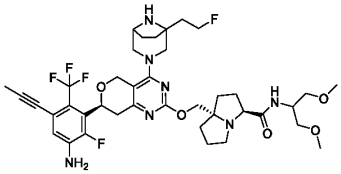
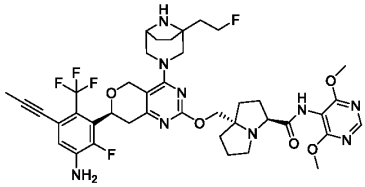
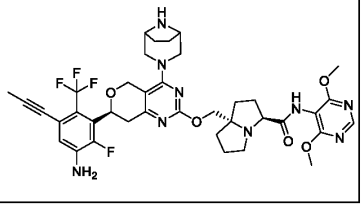
Example S82 	Example S83 	Example S84 
Example S85 	Example S86A/S86B 	Example S87 
Example S88A/S88B 	Example S89A/S89B 	Example S90 
Example S91 	Example S92 	Example S93 
Example S94A/S94B 	Example S95 	Example S96 

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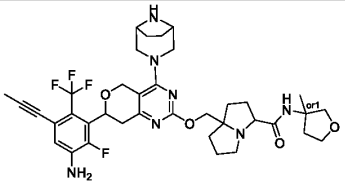
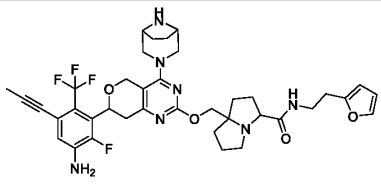
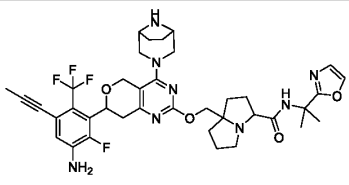
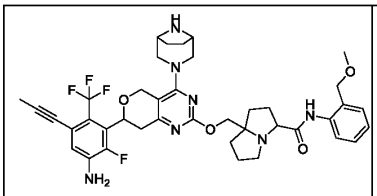
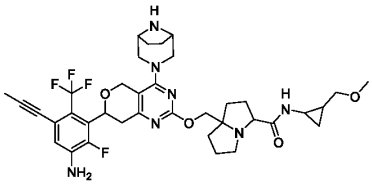
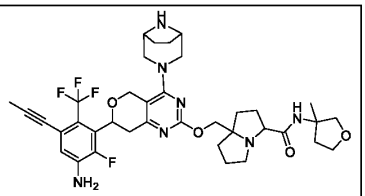
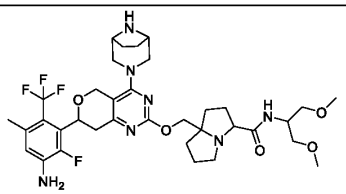
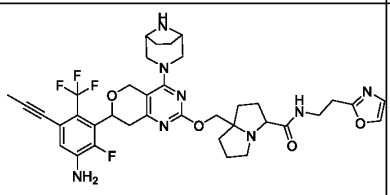
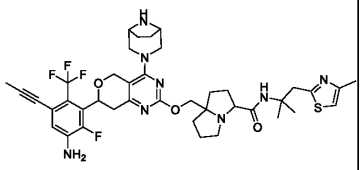
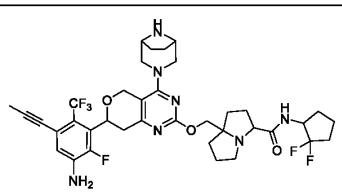
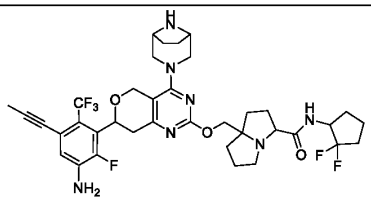
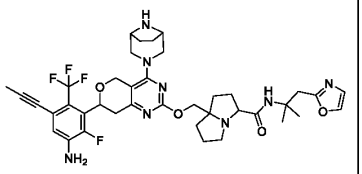
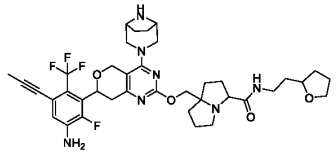
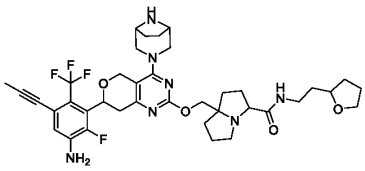
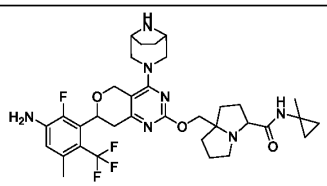
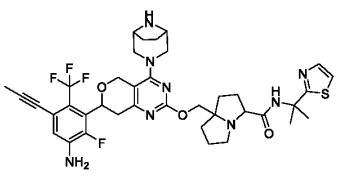
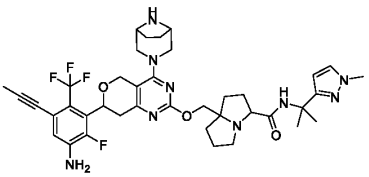
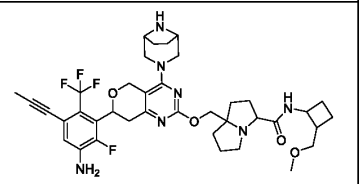
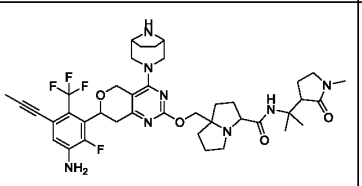
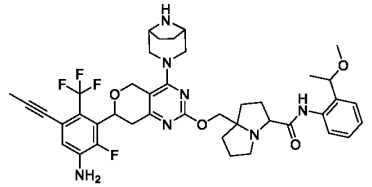
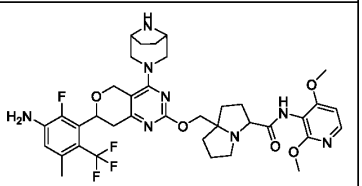
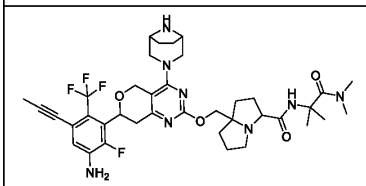
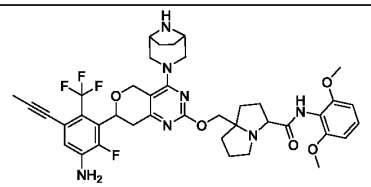
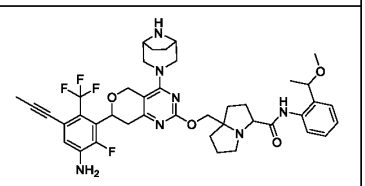
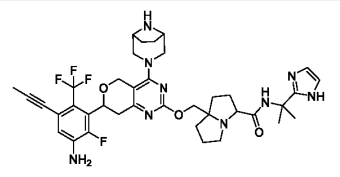
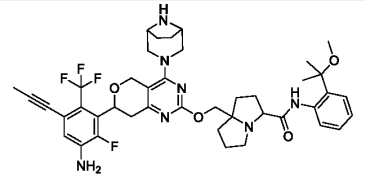
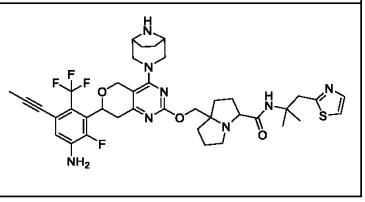
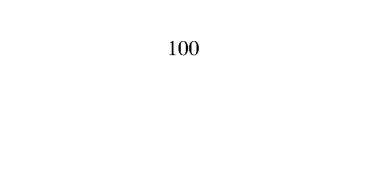
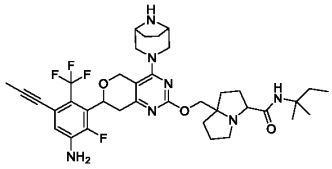
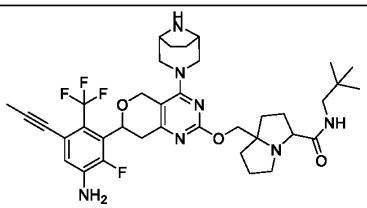
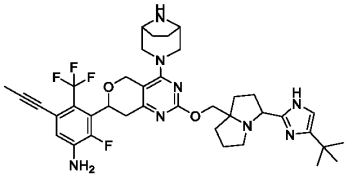
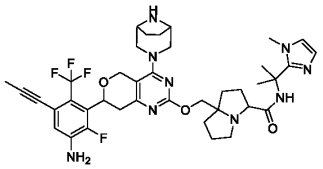
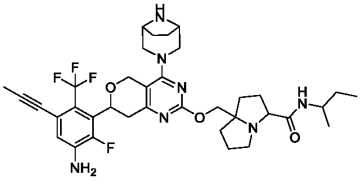
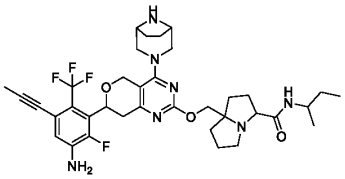
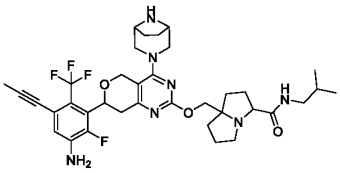
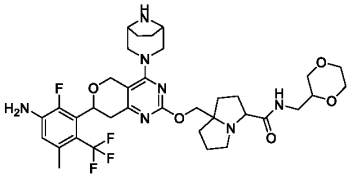
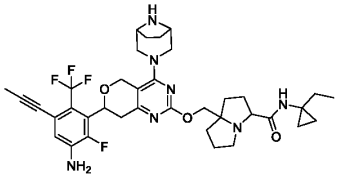
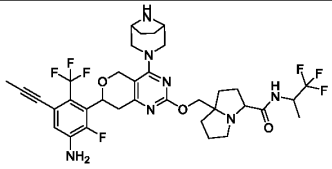
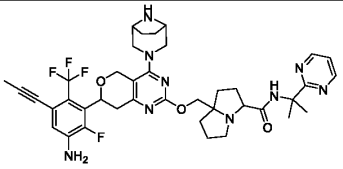
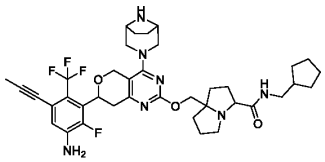
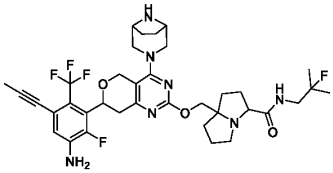
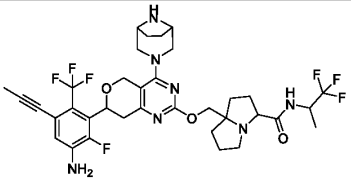
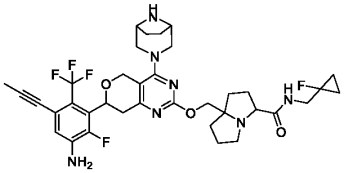
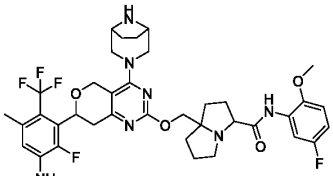
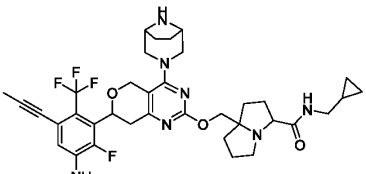
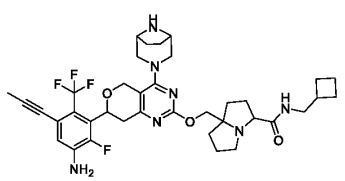
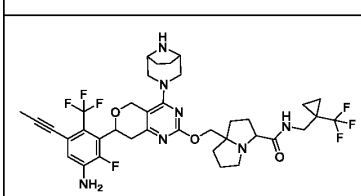
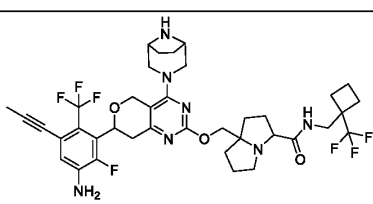
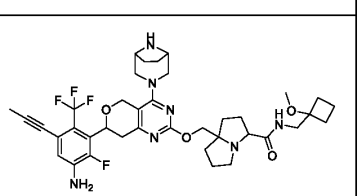
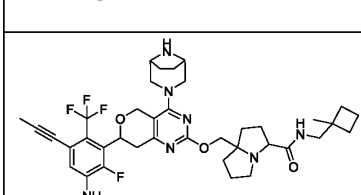
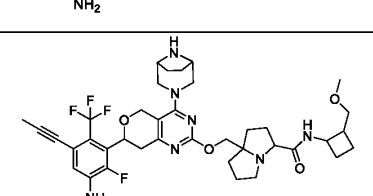
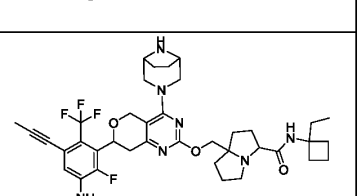
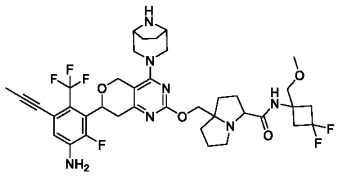
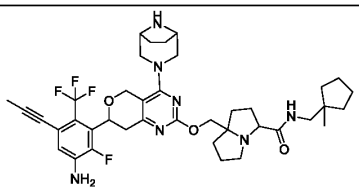
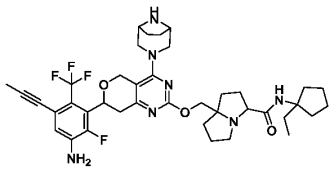
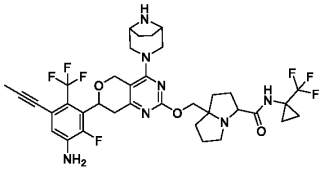
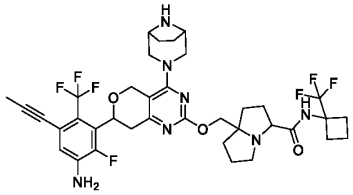
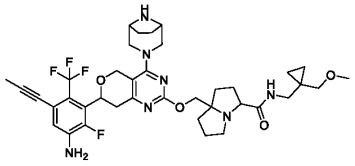
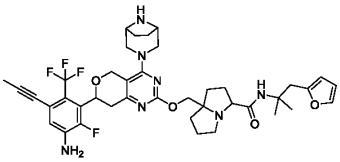
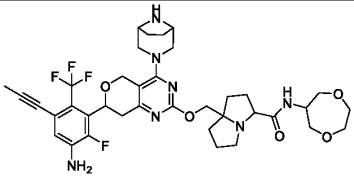
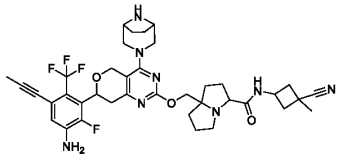
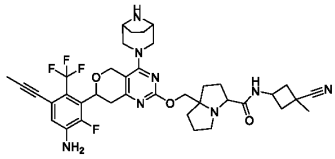
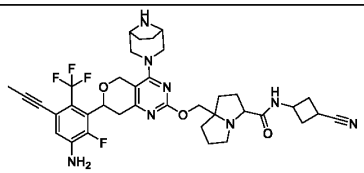
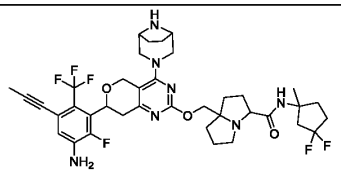
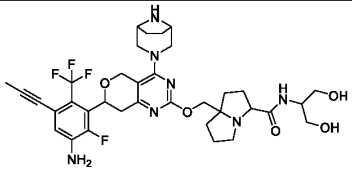
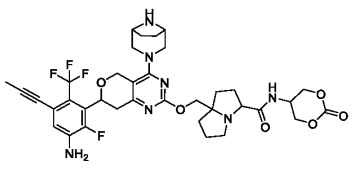
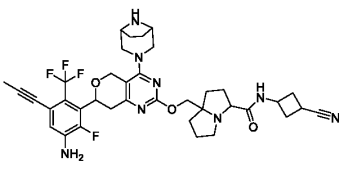
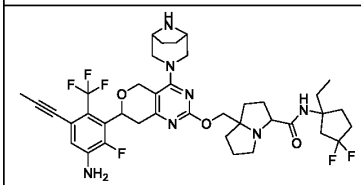
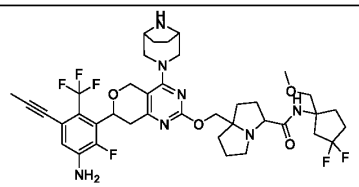
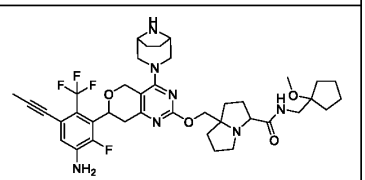
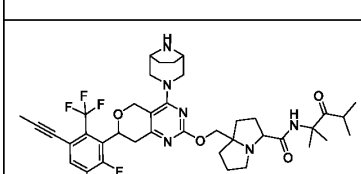
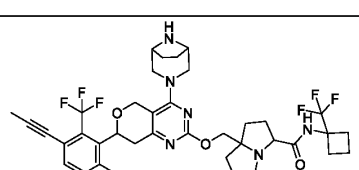
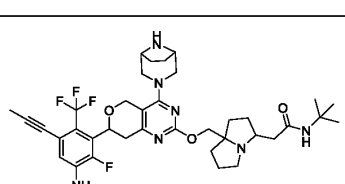
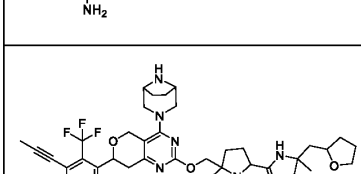
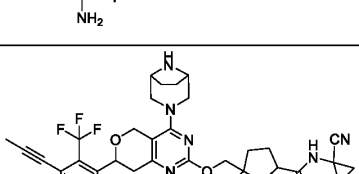
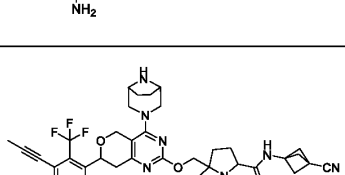
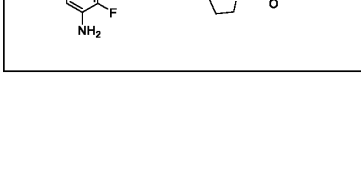
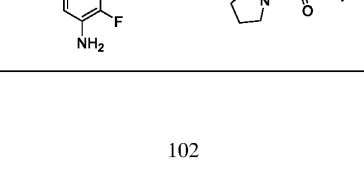
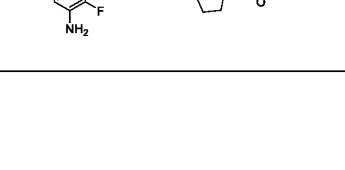
Table 5a

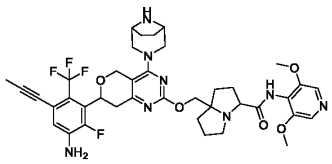
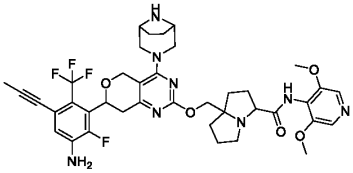
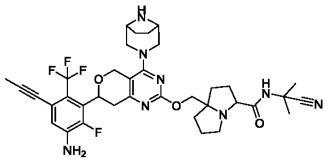
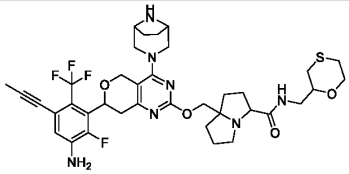
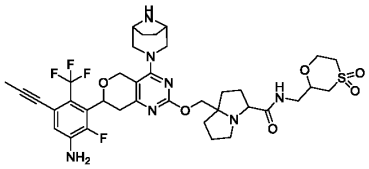
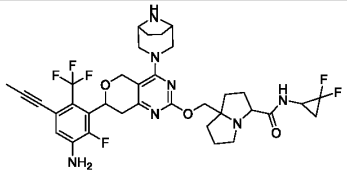
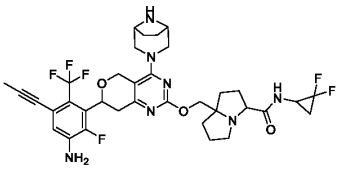
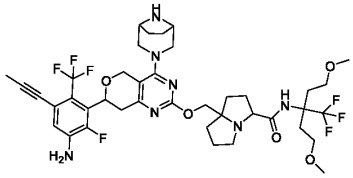
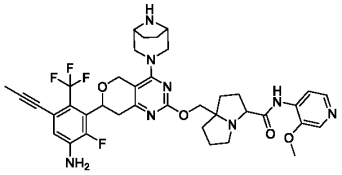
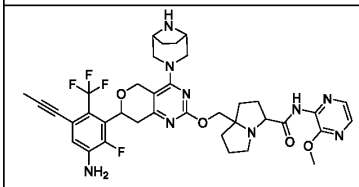
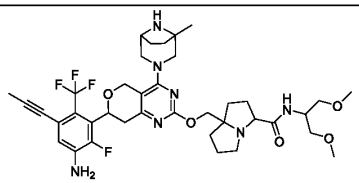
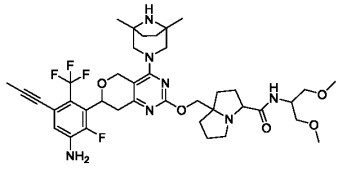
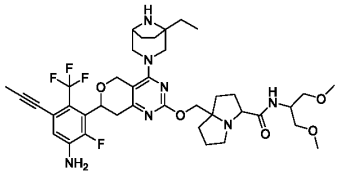
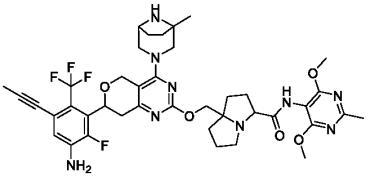
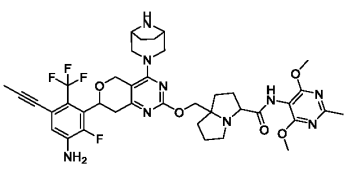
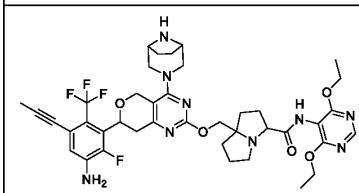
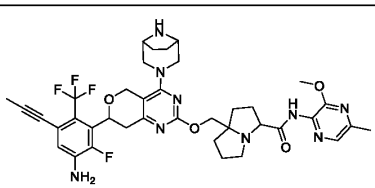
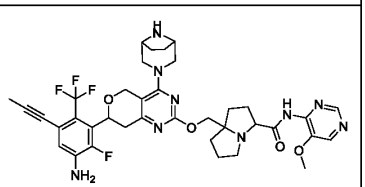
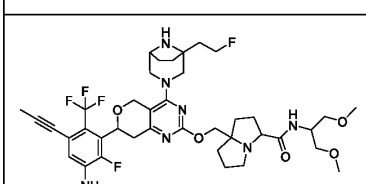
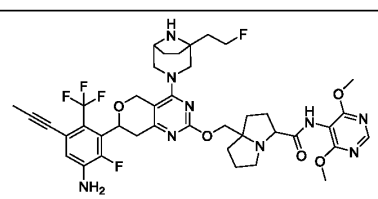
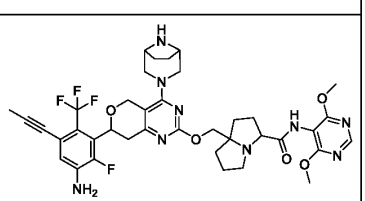
		
		
		
		
		
		
		
		

Table 6

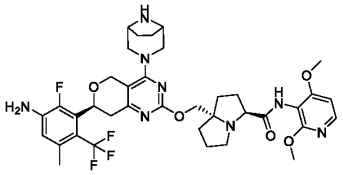
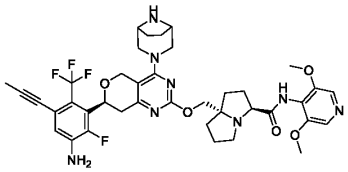
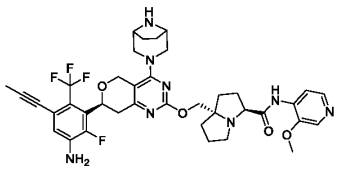
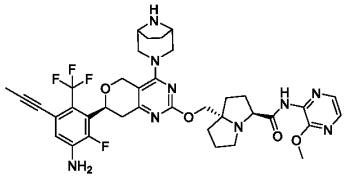
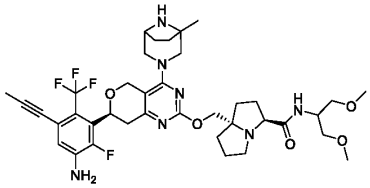
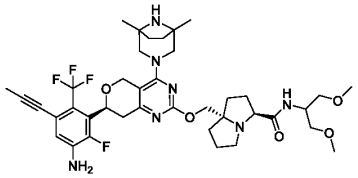
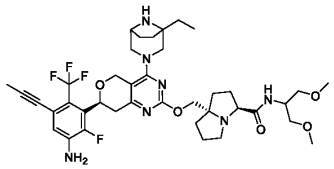
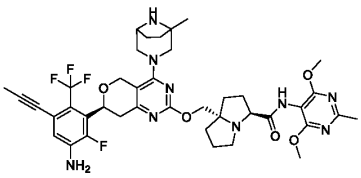
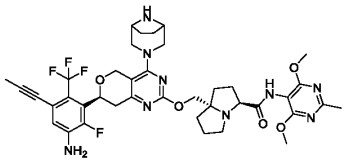
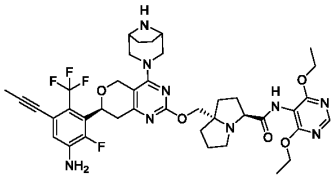
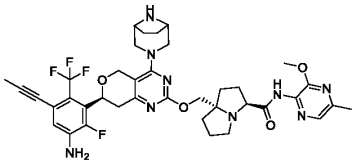
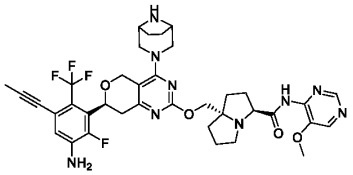
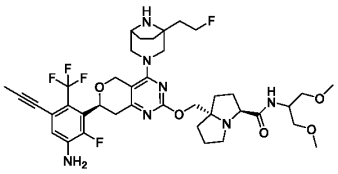
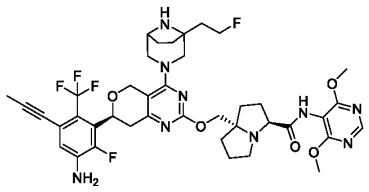
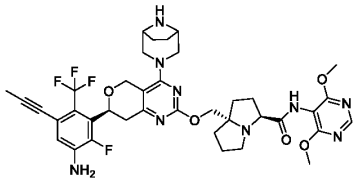
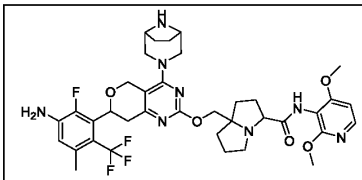
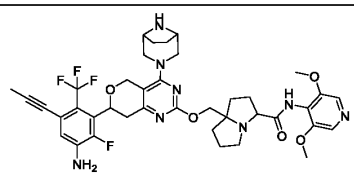
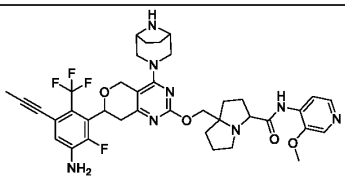
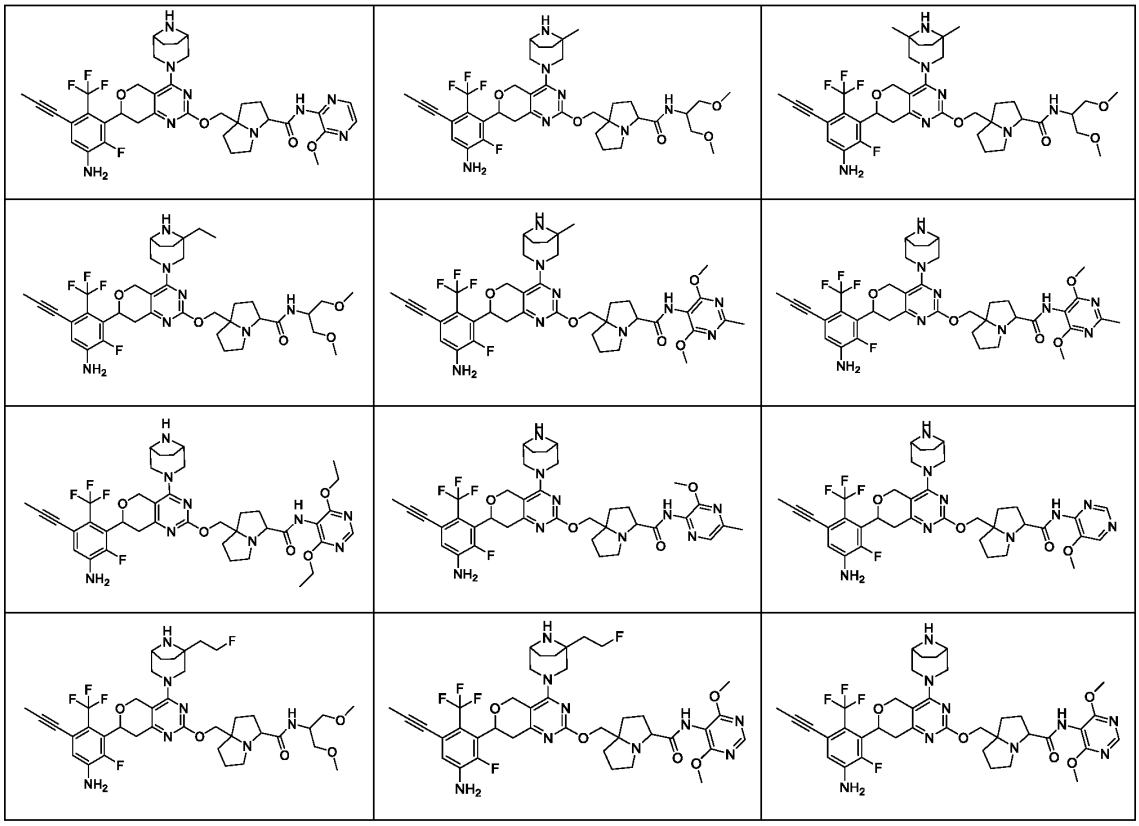
Example S21 	Example S77 	Example S84 
Example S85 	Example S86A/S86B 	Example S87 
Example S88A/S88B 	Example S89A/S89B 	Example S90 
Example S91 	Example S92 	Example S93 
Example S94A/S94B 	Example S95 	Example S96 

Table 6a



In some embodiments, the compound of the present disclosure is a compound selected from Table 1, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 2, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 2a, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 3, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 4, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 5, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 5a, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from

Table 6, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of the present disclosure is a compound selected from Table 6a, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

In certain aspects, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof, comprising administering to the subject a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof (e.g., in a therapeutically effective amount).

In certain aspects, the present disclosure provides methods of treating a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof, comprising administering to the subject a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof (e.g., in a therapeutically effective amount).

In certain aspects, the present disclosure provides uses of a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

In certain aspects, the present disclosure provides uses of a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or disorder (e.g., a disease or disorder associated with dysregulation and/or mutation of KRAS) in a subject in need thereof.

Definitions

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific

terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Unless otherwise specified, the following terms and phrases used herein are intended to have the following meanings. A particular term or phrase should not be considered indeterminate or unclear unless specifically defined, but should be understood in its ordinary meaning. When a trade name appears herein, it is intended to refer to its corresponding commercial product or its active ingredient.

The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

The term “pharmaceutically acceptable” is used herein for those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, and commensurate with a reasonable benefit/risk ratio.

The term “pharmaceutically acceptable salt” refers to a salt of the compound disclosed herein, which is prepared from the compound having particular substituents disclosed herein and a relatively non-toxic acid or base. When the compound of the present disclosure contains a relatively acidic functional group, a base addition salt may be obtained by contacting such a compound with a sufficient amount of a base in a pure solution or a suitable inert solvent. When the compound of the present disclosure contains a relatively basic functional group, an acid addition salt may be obtained by contacting such a compound with a sufficient amount of an acid in a pure solution or a suitable inert solvent. Certain specific compounds disclosed herein contain both basic and acidic functional groups that allow the compounds to be converted into either base or acid addition salts.

The pharmaceutically acceptable salts of the present disclosure may be synthesized from a parent compound containing acid radicals or bases by means of conventional chemical methods. In general, such salts are prepared by the following method: the free acid or base form of the compound reacting with a stoichiometric amount of the appropriate base or acid in water or an organic solvent or a mixture thereof.

The compound of the present disclosure may have a specific geometric or stereoisomeric form. All such compounds are contemplated herein, including cis and trans isomers, (−)- and (+)-

enantiomers, (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, and racemic mixtures and other mixtures thereof, such as enantiomer or diastereomer enriched mixtures, all of which are encompassed within the scope of the present disclosure. Substituents such as alkyl may have an additional asymmetric carbon atom. All these isomers and mixtures thereof are encompassed within the scope of the present disclosure.

The compound disclosed herein may contain an unnatural proportion of atomic isotope at one or more of the atoms that constitute the compound. For example, the compound may be labeled with a radioisotope, such as tritium (^{3}H), iodine-125 (^{125}I), or C-14 (^{14}C). Citing another example, hydrogen may be substituted by deuterium to form a deuterated drug, and the bond formed by deuterium and carbon is firmer than that formed by common hydrogen and carbon. Compared with an un-deuterated drug, the deuterated drug has the advantages of reduced toxic side effect, increased stability, enhanced efficacy, prolonged biological half-life and the like. All isotopic variations of the compound described herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

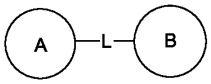
The terms of "optional" or "optionally" means that the subsequently described event or circumstance may, but not necessarily, occur, and the description includes instances where the event or circumstance occurs and instances where it does not.

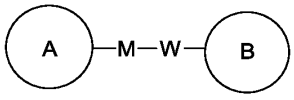
The term "substituted" means that one or more hydrogen atoms on a specific atom are substituted by substituent(s), of which the substituent group may include deuterium and hydrogen variants, as long as the valence of the specific atom is normal and the substituted compound is stable. When the substituent is an oxygen or oxo (i.e., =O), it means that two hydrogen atoms are substituted. The term "optionally substituted" means that an atom may or may not be substituted. Unless otherwise specified, the type and number of the substituents may be arbitrary as long as being chemically achievable.

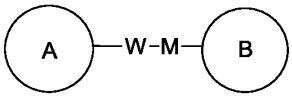
When any variable (e.g., R) occurs more than once in the constitution or structure of a compound, the definition of the variable in each case is independent. Thus, for example, if a group is substituted by 0-2 R, the group may be optionally substituted by two R at most, and the definition of R in each case is independent. Furthermore, a combination of a substituent and/or a variant thereof is permissible only if the combination can result in a stable compound.

When the number of a linking group is 0, such as -(CRR)$_0$-, it means that the linking group is a single bond.

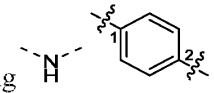
When one of the variables is selected from a single bond, it means that the two groups to which it is connected are directly connected. For example, when L represents a single bond in A-L-Z, it means that the structure is actually A-Z.

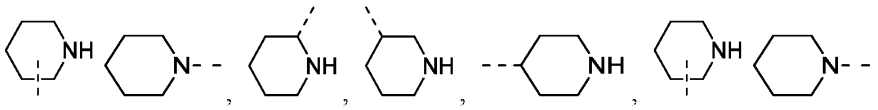
When the listed linking group does not indicate its connection direction, its connection direction is arbitrary, for example, the middle linking group L in 

is -M-W-, at which point -M-W- can be composed of ring A and ring B in the same direction as the reading order from left to right 

, or ring A and ring B in the opposite direction as the reading order from left to right 

. A combination of the linking group, a substituent and/or a variant thereof is permissible only if the combination can result in a stable compound.

Unless otherwise specified, when a group has one or more linkable sites, any one or more sites of the group may be linked to other groups by a chemical bond. When the chemical bond is attached in a manner that is not localized, and the H atom is present at the linkable site, the number of H atoms at the site is correspondingly reduced to a corresponding valency group with the number of chemical bonds attached. The chemical bond to which the site is attached to other groups may be represented by a straight solid bond (), a straight dotted bond ( ), or a wavy line (). For example, a straight solid bond in -OCH_3 indicates that the oxygen atoms in the group are connected to other groups; a straight dotted bond in indicates that the nitrogen atoms at both ends in the group are connected to other groups; a wavy line in indicates that the carbon atoms at positions 1 and 2 in the phenyl group are connected to other groups; indicates that any attachable site on the piperidine group can be connected to other groups by at least 1 chemical bond, including 



at least 4 ways of attachment. Even if H atoms are drawn on -N-, the group in this connection mode is still included, but when 1 chemical bond is connected, the H of the site will correspondingly reduce 1 to the corresponding monovalent piperidine group.

Unless otherwise stated, the absolute configuration of a stereogenic center is represented by a wedged solid bond () and a wedged dashed bond (cid:) and the relative configuration of a stereogenic center is represented by a straight solid bond ( ) and a straight dashed bond ( ). A wavy line ( ) represents a wedged solid bond ( ) or a wedged dashed bond ( ), or a wavy

line ( ) represents a straight solid bond (cid:) or a straight dashed bond ( ).

Unless otherwise stated, when a double bond structure is present in a compound, such as a carbon double bond, a carbon nitrogen double bond, and a nitrogen double bond, and each atom on the double bond is connected with two different substituents (in a double bond comprising a nitrogen atom, a pair of lone pairs of electrons on the nitrogen atom are considered one substituent to which it is connected), a mixture of two isomers of the compound is represented if the atom on the double bond is  represented between the atom and the substituent in the compound.

Unless otherwise stated, the term "tautomer" or "tautomeric form" means that different functional isomers are in dynamic equilibrium at room temperature and may be rapidly converted into each other. Where tautomerization is possible (e.g., in solution), the chemical equilibrium of tautomers may be achieved. For example, a proton tautomer (also known as a prototropic tautomer) includes the interconversion by proton transfer, such as keto-enol isomerization and imine-enamine isomerization. A valence isomer includes the interconversion by recombination of some bonding electrons. A specific example of the keto-enol tautomerization is the interconversion between tautomers pentane-2,4-dione and 4-hydroxypent-3-en-2-one.

Unless otherwise stated, the term "enriched with one isomer", "isomer enriched", "enriched with one enantiomer", or "enantiomer enriched" means that the content of one of the isomers or enantiomers is less than 100% and more than or equal to 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%.

Unless otherwise stated, the term "isomeric excess" or "enantiomeric excess" refers to the difference between the relative percentages of two isomers or enantiomers. For example, if the content of one isomer or enantiomer is 90% and the content of the other isomer or enantiomer is 10%, the isomeric or enantiomeric excess (ee value) is 80%.

Unless otherwise stated, C_{n-n+m} or C_n-C_{n+m} includes any one of the specific cases of n to n+m carbon atoms. For example, C_{1-12} includes C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12}. Also, any range within n to n+m may be included. For example, C_{1-12} includes C_{1-3}, C_{1-6}, C_{1-9}, C_{3-6}, C_{3-9}, C_{3-12}, C_{6-9}, C_{6-12} and C_{9-12}, etc. Similarly, n-n+m membered means that the number of atoms on the ring is n to n+m. For example, 3-12 membered ring includes 3 membered ring, 4 membered ring, 5 membered ring, 6 membered ring, 7 membered ring, 8 membered ring, 9 membered ring, 10 membered ring, 11 membered ring and 12 membered ring. n-n+m membered also represents any range within n to n+m. For example, 3-12 membered ring includes 3-6 membered ring, 3-9 membered ring, 5-6 membered ring, 5-7 membered ring, 6-7 membered ring, 6-8 membered ring, 6-10 membered ring, etc.

The term "halo" or "halogen," by itself or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

Unless otherwise stated, the term "C_{1-n} alkyl" refers to a straight-chained or branched saturated hydrocarbon group consisting of 1 to n (e.g., 4, 5, or 6) carbon atoms. For example, when n is 6, C_{1-n} alkyl includes C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, C_{5-6}, C_6, C_5, C_4, C_3, C_2, and C_1 alkyl, etc. Examples of C_{1-6} alkyl include, but are not limited to, methyl (Me), ethyl (Et), propyl (including *n*-propyl and *i*-propyl), butyl (including *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl), pentyl (including *n*-pentyl and *i*-pentyl), hexyl, and the like.

Unless otherwise specified, the term "C_{1-n} alkoxy" or "C_{1-n} alkyoxy" denotes alkyl groups containing 1 to n (e.g., 4, 5, or 6) carbon atoms that are attached to the remainder of the molecule by one oxygen atom. For example, when n is 6, C_{1-n} alkoxy includes C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, C_{5-6}, C_6, C_5, C_4, C_3, C_2, and C_1 alkoxy, etc. Examples of C_{1-6} alkoxy include, but are not limited to, methoxy, ethoxy, propoxy (including *n*-propoxy and *i*-propoxy), butoxy (including *n*-butoxy, *i*-butoxy, *s*-butoxy, and *t*-butoxy), pentoxy (including *n*-pentoxy and *i*-pentoxy), hexyloxy, and the like.

Unless otherwise specified, the term "C_{1-n} alkylamino" denotes -NH-C_{1-n} alkyl groups. For example, when n is 3, C_{1-n} alkylamino include, but are not limited to, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH_2(CH_3)_2$, etc.

Unless otherwise specified, the term "di-C_{1-n} alkylamino" denotes $-N(C_{1-n}\text{ alkyl})_2$ groups. For example, when n is 3, di-C_{1-n} alkylamino include, but are not limited to, $-N(CH_3)_2$ and $-N(CH_3)CH_2CH_3$.

Unless otherwise stated, "C_{2-n} alkenyl" refers to a straight-chained or branched hydrocarbon group consisting of 2 to n carbon atoms containing at least one carbon-carbon double bond, which may be located anywhere in the group. For example, when n is 4, C_{2-n} alkenyl group includes C_{2-4}, C_{2-3}, C_{3-4}, C_4, C_3, and C_2 alkenyl, etc.. Examples of C_{2-4} alkenyl include, but are not limited to, vinyl, allyl, butenyl, butadienyl, and the like.

Unless otherwise stated, "C_{2-n} alkynyl" refers to a straight-chained or branched hydrocarbon group consisting of 2 to n carbon atoms containing at least one carbon-carbon triple bond, which may be located anywhere in the group. For example, when n is 4, C_{2-n} alkynyl groups include C_{2-4}, C_{2-3}, C_{3-4}, C_4, C_3, and C_2 alkynyl, etc.. Examples of C_{2-4} alkynyl include, but are not limited to, ethynyl, propynyl, butynyl, and the like.

Unless otherwise specified, "C_{3-n} cycloalkyl" refers to a saturated cyclic hydrocarbon group consisting of 3 to n carbon atoms that includes a monocyclic, bicyclic, and tricyclic system, wherein the bicyclic and tricyclic systems include a spiro ring, a parallel ring, and a bridging ring. When n is

10, C_{3-n} cycloalkyl includes C_{3-10}, C_{3-9}, C_{3-8}, C_{3-7}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-10}, C_{4-9}, C_{4-8}, C_{4-7}, C_{4-6}, C_{4-5}, ... C_{9-10}, C_{10}, C_9, C_8, C_7, C_6, C_5, C_4, etc.. Examples of C_{3-10} cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, ice-lowering alkyl, [2.2.2]dicyclooctane etc.

Unless otherwise specified, the term "heterocyclyl" denotes a saturated or partially unsaturated cyclic group, of which one or more ring atoms being heteroatoms independently selected from O, S, and N, the remaining being carbon atoms, wherein the carbon atoms are optionally substituted with oxygen (i.e., C(O)), the nitrogen atoms are optionally quaternized, the nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., NO and $S(O)_p$, p is 1 or 2). "Heterocyclyl" may be monocyclic or multicyclic (including spiro-, bridged-, and fused-ring system), and may comprise 3- to 10-membered ring or rings. Examples of heterocyclyl groups include, but are not limited to, azetidyl, oxetyl, thiobutyl, pyrrolidinyl, pyrazolyl, imidazoalkyl, tetrahydrothienyl (including tetrahydrothien-2-yl and tetrahydrothien-3-yl, etc.), tetrahydrofuranyl (including tetrahydrofuran-2-yl, etc.), piperidinyl (including 1-piperidinyl, 2-piperidinyl and 3-piperidinyl, etc.), piperazinyl (including 1-piperazinyl and 2-piperazinyl etc.), morpholinyl (including 3-morpholinyl and 4-morpholinyl, etc.), dioxanyl, dithianyl, isooxazolidyl, isothiazolidyl, 1,2-oxazinyl, 1, 2-thiazinyl, or hexahydropyridazinyl, or the like. In the case of multicyclic heterocyclyl, only one of the rings in the heterocyclyl needs to be non-aromatic (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl, benzo[d][1,3]dioxole, 2,3-dihydrobenzo[b][1,4]dioxine, 2,3-dihydrobenzofuran, and the like).

Unless otherwise specified, the terms "C_{6-10} aromatic ring" and "C_{6-10} aryl" are used interchangeably, and refer to a cyclic hydrocarbon group having a conjugated π electron system consisting of 6 to 10 carbon atoms, which may be a monocyclic, fused bicyclic, or fused tricyclic system, wherein each ring is aromatic. C_{6-10} aryl includes C_{6-9}, C_9, C_{10}, and C_6 aryl etc. Examples of C_{6-10} aryl groups include, but are not limited to, phenyl, naphthyl (including 1-naphthyl and 2-naphthyl, etc.).

Unless otherwise specified, the terms "heteroaryl ring" and "heteroaryl" are used interchangeably, and refer to a cyclic group representing a conjugated π electron system and may comprise 5-10 membered ring or rings, of which one or more ring atoms are heteroatoms independently selected from O, S, and N, and the rest of which are carbon atoms. It can be a monocyclic, fused bicyclic, or fused tricyclic system comprising one, two, or more rings, where each ring is aromatic, wherein the nitrogen atoms are optionally quaternized, the nitrogen and sulfur heteroatoms could optionally be oxidized (i.e. NO and $S(O)_p$, p is 1 or 2). Examples of heteroaryl include, but are not limited to, pyrrolyl (including *N*-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl, etc.),

pyrazolyl (including 2-pyrazolyl and 3-pyrazolyl, etc.), imidazolyl (including *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, and 5-imidazolyl, etc.), oxazolyl (including 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl, etc.), triazolyl 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl and 4*H*-1,2,4-triazoly etc.), tetrazolyl, isoxazolyl (3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl etc.), thiazolyl (including 2-thiazolyl, 4-thiazolyl and 5-thiazolyl etc.), furanyl (including 2-furanyl and 3-furanyl, etc.), thiophenyl (including 2-thiophenyl and 3-thiophenyl, etc.), pyridinyl (including 2-pyridinyl, 3-pyridinyl and 4-pyridinyl, etc.), pyrazinyl, pyridinyl (including 2-pyridinyl and 4-pyridinyl, etc.), benzothiazolyl (including 5-benzothiazolyl, etc.), purinyl, benzimidazolyl (including 2-benzoimidazolyl, etc.), benzoxazolyl, indolyl (including 5-indolyl, etc.), isoquinolinyl (including 1-isoquinolinyl and 5-isoquinolinyl, etc.), quinoxolinyl (including 2-quinoxolinyl and 5-quinoxolinyl, etc.), or quinolinyl (including 3-quinoline and 6-quinoline, etc.), or the like.

The compound of the present disclosure may be prepared by a variety of synthetic methods well known to those skilled in the art, including the following enumerative embodiment, the embodiment formed by the following enumerative embodiment in combination with other chemical synthesis methods and the equivalent replacement well known to those skilled in the art. The preferred embodiment includes, but is not limited to the embodiment of the present disclosure.

The structure of the compound of the present disclosure may be confirmed by conventional methods well known to those skilled in the art, and if the present disclosure relates to the absolute configuration of the compound, the absolute configuration may be confirmed by conventional technical means in the art. For example, single crystal X-ray diffraction (SXRD) may be used, wherein a cultured single crystal is analyzed by a Bruker D8 Venture diffractometer to collect diffraction intensity data, and the light source is CuKα radiation, and the scanning mode is: φ/ω scanning; and after relevant data are collected, the crystal structure is further analyzed by using a direct method (Shelxs97), so that the absolute configuration can be confirmed.

The solvents used in the present disclosure are commercially available. The present disclosure uses the following abbreviations: NaOH stands for sodium hydroxide; DMF stands for N,N-dimethylformamide; THF stands for tetrahydrofuran; 2-MeTHF stands for 2-methyl tetrahydrofuran; DCM stands for dioxane; EA stands for ethyl acetate; DIPEA stands for N,N-diisopropylethylamine; DCM stands for dichloroperoxybenzoic acid; m-CPBA stands for m-chloroperoxybenzoic acid; Boc_2O stands for di-tert-butyl carbonic anhydride; $LiAlH_4$ stands for lithium tetrahydroxium; MnO_2 stands for manganese dioxide; NBS stands for N-bromosuccinimide; TMP stands for trimethylpropane; n-BuLi stands for n-butyl lithium; TFA stands for trifluoroacetic acid; Xphos Pd G4 stands for: (SP-4-3)[dicyclohexyl[2',4',6'-tris(isopropyl)[1,1'-biphenyl]-2-yl]phosphine](methanesulfonic acid)[2'-(methylamino)[1,1'-biphenyl]-2-yl]palladium; $AgNO_3$

stands for silver nitrate; NCS stands for N-chlorosuccinimide.

Compounds are named according to conventional nomenclature in the art or using ChemDraw® software, and supplier's catalog names are adopted for commercially available compounds.

The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof or a composition to a subject, which can form an equivalent amount of active compound within the subject's body.

A "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

An "effective amount" or "therapeutically effective amount" when used in connection with a compound or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition is an amount effective for treating or preventing a disease in a subject as described herein.

The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

The compounds of the present disclosure, or a pharmaceutically acceptable salt, thereof, can also be used to prevent a disease, condition or disorder. As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

As used herein, a KRAS mutation-associated disease or disorder, or a disease or disorder associated with dysregulation and/or mutation of KRAS means any disease or other deleterious condition in which a mutation of or dysregulation or disruption of the function of KRAS plays a role. Accordingly, another embodiment of the present disclosure relates to treating or lessening the severity of one or more diseases in which a mutation of or dysregulation or disruption of the function of KRAS plays a role. Specifically, the present disclosure relates to a method of treating or lessening the severity of a disease or condition as described herein, wherein said method comprises administering to a subject in need thereof a compounds of the present disclosure (e.g., a compound of any of the formulae or any individual compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, or a composition according to the present disclosure.

In some embodiments, the KRAS mutation is a KRAS G12D, G12C, or G12V mutation.

In some embodiments, the KRAS mutation is a KRAS G12D mutation.

In some embodiments, the KRAS mutation is a KRAS G12C mutation.

In some embodiments, the KRAS mutation is a KRAS G12V mutation.

The present disclosure also provides preparation of drugs for treating KRAS mutation-associated diseases or disorders, using the compounds or stereoisomers thereof, or pharmaceutically acceptable salts thereof disclosed herein.

The present disclosure also provides the use of the compounds or stereoisomers thereof, or pharmaceutically acceptable salts thereof disclosed herein for the treatment of a KRAS mutation-associated disease or disorder.

The present disclosure also provides the compounds or stereoisomers thereof, or pharmaceutically acceptable salts thereof disclosed herein for use in the manufacture of a medicament for the treatment of a KRAS mutation-associated disease or disorder.

The present disclosure also provides a method of treating a disease or disorder associated with a KRAS mutation, comprising administering to a subject in need thereof the compounds or stereoisomers thereof, or pharmaceutically acceptable salts thereof disclosed herein.

The present disclosure also provides a pharmaceutical composition comprising a compound of the present disclosure (e.g., a compound of any of the formulae or any individual compounds disclosed herein) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient or carrier.

A "pharmaceutical composition" is a formulation containing the compound of the present disclosure in a form suitable for administration to a subject. In some embodiments, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (e.g., a formulation of the disclosed compound or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In some embodiments, the active

compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

A pharmaceutical compositions of the disclosure are formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), and transmucosal administration.

The present disclosure also provides the following biological test methods:

Test method 1. GP2D cell p-ERK inhibition test

1. Purpose

By HTRF, compounds that effectively inhibited p-ERK in ^{G12D}D mutant GP2D cells were screened.

2. Experimental process

1). GP2D cells were seeded in a transparent 96-well cell culture plate, with 80 μL of cell suspension per well, containing 8,000 cells per well. The cell plate was placed in a carbon dioxide incubator and incubated overnight at 37°C;

2). Take 2 μL of compound and add 78 μL of cell culture medium, mix well, take 20 μL of compound solution and add it to the corresponding cell plate wells, and place the cell plate back in the carbon dioxide incubator for continued incubation for 1 hours;

3). After the end of incubation, discard the cell supernatant and add 50 μL of 1X cell lysate to each well, and incubate at room temperature with shaking for 30 minutes;

4). Use detection buffer to dilute Phospho-ERK1/2 Eu Cryptate antibody and Phospho-ERK1/2 d2 antibody by 20 times;

5). Take 16 μL of cell lysate supernatant into a new 384 white microplate, add 2 μL of Phospho-

ERK1/2 Eu Cryptate antibody diluent and 2 μL of Phospho-ERK1/2 d2 antibody diluent, and incubate at room temperature for at least 4 hours;

6). After the end of incubation, use a multi-label analyzer to read HTRF excitation: 320 nm, emission: 615 nm, 665 nm;

7). Calculate the compound to be tested IC_{50}.

Test method 2. AGS cell p-ERK inhibition test

1. Purpose

By HTRF, compounds that effectively inhibit p-ERK in $KRAS^{G12D}$ mutant AGS cells were screened.

2. Experimental process

1). AGS cells were seeded in a transparent 96-well cell culture plate, with 80 μL of cell suspension per well, containing 10,000 cells per well. The cell plate was placed in a carbon dioxide incubator and incubated overnight at 37°C;

2). At the end of incubation, discard the cell supernatant, add 80 μL of culture medium per well, the culture medium contains 0.02% serum, place the cell plate in a carbon dioxide incubator, and incubate overnight at 37°C;

3). Take 2 μL of compound and add 78 μL of cell culture medium, mix well, take 20 μL of compound solution and add it to the corresponding cell plate wells, and place the cell plate back in the carbon dioxide incubator for continued incubation for 3 hours;

4). After the end of incubation, discard the cell supernatant and add 50 μL of 1X cell lysate to each well, and incubate at room temperature with shaking for 30 minutes;

5). Use detection buffer to dilute Phospho-ERK1/2 Eu Cryptate antibody and Phospho-ERK1/2 d2 antibody by 20 times;

6). Take 16 μL of cell lysate supernatant into a new 384 white microplate, add 2 μL of Phospho-ERK1/2 Eu Cryptate antibody diluent and 2 μL of Phospho-ERK1/2 d2 antibody diluent, and incubate at room temperature for at least 4 hours;

7). After the end of incubation, use a multi-label analyzer to read HTRF excitation: 320 nm, emission: 615 nm, 665 nm;

8). Calculate the compound to be tested IC_{50}.

Test method 3. Anti-cell proliferation of compounds in tumor cell line AsPC-1

Study objectives

In this experiment, the effect of compound on cell proliferation was investigated by detecting the effect of compound on in vitro cell activity in $KRAS^{G12D}$ mutant tumor cell line AsPC-1.

Experimental Materials

Cell line: AsPC-1; tumor type: Pancreatic cancer; Growth characteristics: Adherent growth; culture

method: RPMI 1640 + 10% FBS

Ultra Low Cluster-96 well plate (Corning-7007)

Greiner CELLSTAR 96-well plate (# 655090)

Promega CellTiter-Glo 3D Luminescence Cell Viability Assay Kit (Promega-G9683)

2104-10 EnVision Plate Reader, PerkinElmer

RPMI 1640, DMEM, PBS (phosphate buffer), FBS (fetal bovine serum), antibiotic-antimycotic (antibiotic-antifungal), L-glutamine (L-glutamine), DMSO (dimethyl sulfoxide)

Experimental Methods and Procedures

Cell Culture

Tumor cell lines were incubated in an incubator at 37oC, 5% CO_2 under the culture conditions indicated by the culture method. Periodic passages are performed, and cells in logarithmic growth are taken for plating.

Cell Plating

Cells were stained with Trypan Lang and live cells were counted.

Adjust the cell concentration to the appropriate concentration.

Cell line: AsPC-1; **Density (per well):** 7000 cells.

Add 135 μL of cell suspension to each well of the ULA plate, and add the same volume of cell-free medium to the vehicle control air.

After plating, immediately centrifuge the ULA plate at room temperature for 10 minutes and centrifuge at 1000 rpm. Note: After centrifugation, care must be taken not to cause unnecessary shaking.

Incubate plates overnight in an incubator at 37°C, 5% CO_2, and 100% relative humidity.

Preparation of 10X compound working solution and compound treatment cells (Day 1)

After preparing the 10X compound working solution (DMSO 10X working solution), add 15 μL of 10X compound working solution to the ULA culture plate, and add 15 μL of DMSO-cell culture mixture to the vehicle control and blank control respectively.

The 96-well cell plates were returned to the incubator for incubation for 120 hours.

Cell spheroids were observed daily until the end of the experiment.

CellTiter-Glo Luminescence Cell Viability Assay (Day 5)

The following steps were performed in accordance with the instructions for the Promega CellTiter-Glo 3D Luminescence Cell Viability Assay Kit (Promega # G9683).

Add 150 μL of CellTiter-Glo 3D reagent (equal to the volume of cell culture medium in each well) to

each well. Wrap the cell plate with aluminum foil to protect from light.

Shake the plate on an orbital shaker for 5 minutes.

Carefully pipet up and down 10 times and mix well the mixture. Ensure that the multicellular spheroids are adequately separated before proceeding to the next step.

The solution in the ULA plate was then transferred to a black bottom plate (#655090) and left at room temperature for 25 minutes to stabilize the luminescent signal.

Luminescent signal is detected on the 2104 EnVision reader.

Data analysis

The inhibition rate (IR) of the test compound was calculated by using the following formula: IR (%) = (1 – (RLU compound – RLU vehicle control) / (RLU vehicle control – RLU vehicle control)) * 100%. Inhibition rates were calculated for different concentrations of compounds in Excel, and then plotted with GraphPad Prism software and relevant parameters were calculated, including minimum inhibition, maximum inhibition, and IC_{50}.

Test method 4. Pharmacokinetic Study on Oral and Intravenous Test Compounds in CD-1 Mice

Experimental Purpose

Test the in vivo pharmacokinetics of oral and intravenous compounds in CD-1 mice.

Protocol

The test compound was mixed with 5% DMSO + 95 centrifugal 10% HP-β-CD) aqueous solution, vortexed and sonicated to prepare a 0.5 mg/mL clear solution (intravenous) or a 3 mg/mL clear solution (oral), and the microporous filter membrane was filtered for later use. Male CD-1 mice aged 7 to 10 weeks were selected and intravenously injected with the candidate compound solution. The candidate compound solution was administered orally. Whole blood was collected for a certain period of time, plasma was prepared, drug concentration was analyzed by using the LC-MS/MS method, and pharmacokinetic parameters were calculated by using Phoenix WinNonlin software (Pharsight, USA).

Technical Effect

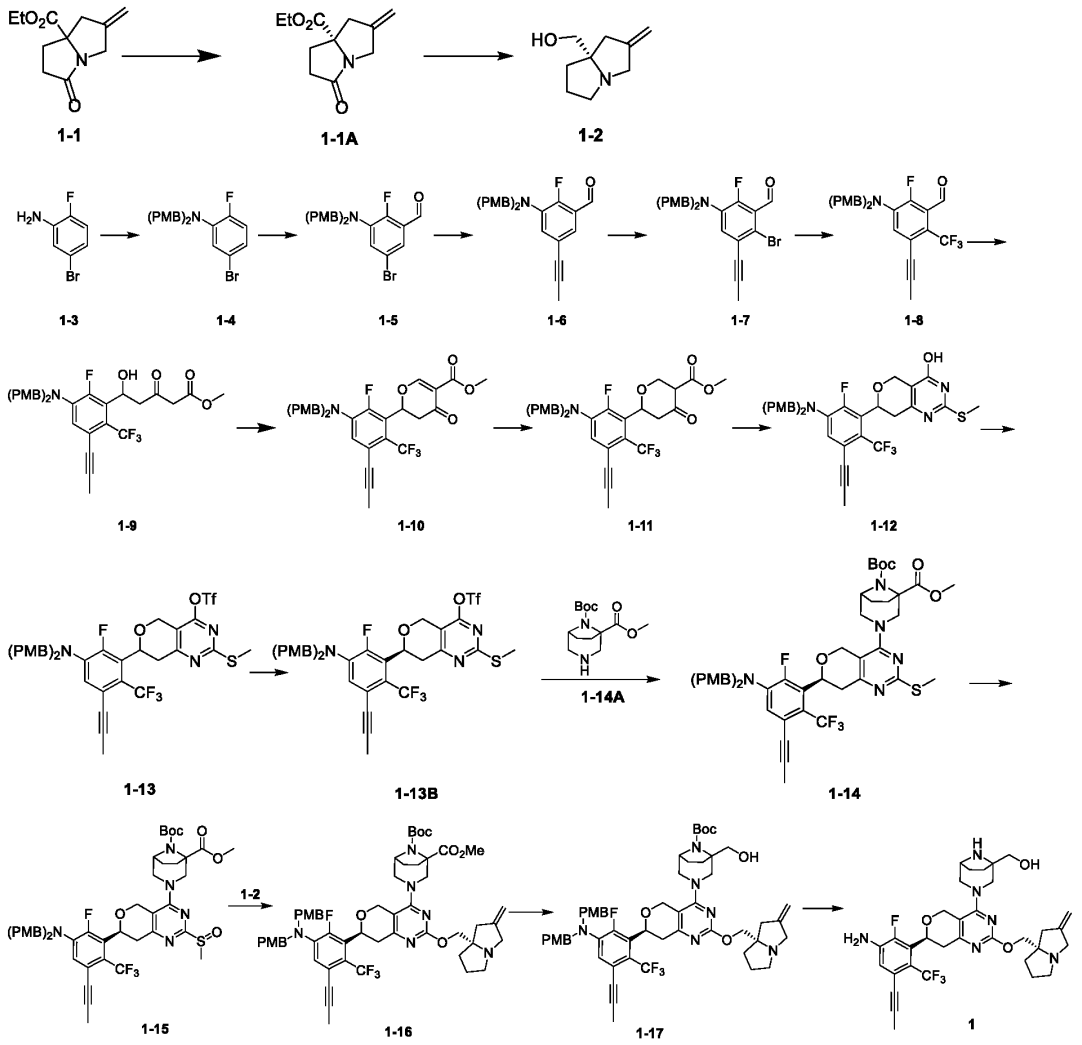
The compound of the present invention has good cell proliferation inhibitory activity on $KRAS^{G12D}$ mutant cells and has significant inhibitory effect on p-ERK of KRASG12D mutant cells.

Examples

The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood

that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Example 1



Step 1

Preparation of supercritical liquid chromatography (SFC) (chromatographic column: ChiralPak IH, 250*50 mm, 10 μm; mobile phase: A: Supercritical carbon dioxide, B: [0.1% ammonia water-ethanol]; B%: 20%-20% running time 3.7 min) to obtain compound **1-1A**, SFC analytical method (column: Chiralpak IH-3, 100 × 4.6 mm I.D., 3 μm; mobile phase: A (supracritical carbon dioxide) and B (ethanol, containing 0.1% isopropylamine); gradient: B% = 10~50%, 4 min; flow rate: 3.4 mL/min; wavelength: 220 nm; pressure: 2000 psi), compound **1-1A**Rt = 1.489 min, ee value 98.82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.99 - 4.86 (m, 2H), 4.26 - 3.95 (m, 3H), 3.59 (m, 1H), 3.00 - 2.88 (m, 1H),

2.87 - 2.12 (m, 4H), 1.91 (s, 1H), 1.20 - 1.08 (m, 3H).

Step 2

Dissolve lithium tetrahydroaluminum (1.55 g, 40.15 mmol) in anhydrous tetrahydrofuran (30 mL), cool to 0°C, add anhydrous tetrahydrofuran (20 mL) solution of compound **1-1A** (2.8 g, 13.38 mmol) under nitrogen protection, and react at 70°C for 1 hour. Add 1.5 mL of water to the reaction solution at 0°C, add 1.5 mL of 15% NaOH solution, add 4.5 mL of water, stir for 20 minutes, filter the reaction solution, wash the filter cake with 10 mL of tetrahydrofuran, and concentrate the filtrate to obtain compound **1-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.99 - 4.86 (m, 2H), 4.26 - 3.95 (m, 3H), 3.59 (m, 1H), 3.00 - 2.88 (m, 1H), 2.74 - 2.27 (m, 4H), 1.91 (s, 1H), 1.20 - 1.08 (m, 3H).

Step 3

Compounds **1-3** (480 g, 2.53 mol) were weighed, DMF (2,500 mL) was added, 4-methoxychlorobenzyl (5.18 mol, 702.79 mL) was added, potassium carbonate (872.82 g, 6.32 mol was added, potassium iodide (419.35 g, 2.53 mol) was reacted at 65°C for 2 hours. Add water (1,000 mL), extract with ethyl acetate (1,000 mL * 3), and concentrate the organic phase under reduced pressure to obtain compound **1-4**, MS m/z = 430.0 $[M+H]^+$.

Step 4

Weigh compound 2,2,6,6-tetramethylpiperidine (220.59 g, 1.56 mol, 265.13 mL), THF (3000 mL) was added, n-butyllithium (2.5 M, 499.73 mL) was added at -5°C, stirred for 0.5 hours, and cooled to -60°C, compound **1-4**280 g, 624.67 mmol was added for 0.5 hours (DMF228.28 g, 3.12 mol, 240.30 mL) was added. The reaction was continued for 0.5 hour. Pour the reaction solution into water (1,000 mL), add 1N hydrochloric acid to adjust the pH to 7, extract with ethyl acetate (1,000 mL * 3), concentrate the organic phase under reduced pressure, and separate by column chromatography (petroleum ether: Ethyl acetate = 10:1) to obtain compounds **1-5**.

Step 5

Weigh Compounds **1-5** (370 g, 807.30 mmol), toluene (1500 mL), dichlorobis[di-tert-butyl-(4-dimethylaminophenyl)phosphine]palladium (2.86 g, 4.04 mmol, 2.86 mL) and add tributyl(1-propynyl)tin (265.69 g, 807.30 mmol), and reacted at 120°C under nitrogen protection for 2 hours. The reaction solution was concentrated under reduced pressure and separated by column chromatography (petroleum ether: Ethyl acetate = 5:1) to obtain compounds **1-6**. MS m/z =418.1 $[M+H]^+$.

Step 6

Compounds **1-6** (450 g, 970.13 mmol) were weighed, DMF (100 mL) was added, N-bromosuccinimide (189.93 g, 1.07 mol) was added, and the solution was reacted at 25°C for 2 hours. N-bromosuccinimide (17.27 g, 97.01 mmol) was added, and the reaction was continued for 3 hours.

The reaction solution was concentrated under reduced pressure and separated by column chromatography (petroleum ether: Ethyl acetate = 5:1) to obtain compounds **1-7**. MS m/z =496.0 $[M+H]^+$.

Step 7

Compounds **1-7** (55 g, 110.81 mmol) were weighed, DMF (300 mL) was added, methyl fluorosulfonyl difluoroacetate (42.57 g, 221.61 mmol, 28.19 mL) was added, copper iodide (42.21 g, 221.61 mmol), and the reaction was carried out under nitrogen protection at 110°C for 2 hours. Add 500 mL of water to quench, extract with ethyl acetate (600 mL*3), combine the extracted organic phases, wash with water (800 mL*2) and saturated brine (800 mL), dry with anhydrous sodium sulfate, filter, and concentrate. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1) to obtain compounds **1-8**. MS m/z =485.9 $[M+H]^+$.

Step 8

For tetrahydrofuran solution (350 mL) of sodium hydrogen (6.34 g, 158.61 mmol, 60% purity), added methyl acetate (158.61 mmol, 17.10 mL) dropwise at 0 °C for 15 minutes. Cool to -20°C and then add n-butyl lithium dropwise (2.5 M, 63.44 mL). After dropwise addition, continue stirring for 15 min, and then add compound **1-8** (35 g, 72.10 mmol) in tetrahydrofuran (350 mL). Reaction 0.5 hour。The reaction was quenched by adding 200 mL of saturated ammonium chloride solution, extracted with ethyl acetate (300 mL*2), combined with the extracted organic phase, washed with saturated brine (400 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1-1:1) to obtain compound **1-9**. MS m/z =624.2 $[M+Na]^+$.

Step 9

Compounds **1-9** (38 g, 63.17 mmol) were weighed, dichloromethane (300 mL) was added, and N,N-dimethylformamide dimethylacetal (9.03 g, 75.80 mmol) was added. Reaction at 25°C for 16 hours. Cool to 0°C, add boron trifluoride diethyl etherate (10.76 g, 75.80 mmol, 9.32 mL), continue stirring at 0°C for 1 hour, add 200 mL of saturated sodium bicarbonate solution to the system, separate the organic phase, extract the aqueous phase with 200 mL of dichloromethane, combine the extracted organic phase, wash with 250 mL of saturated brine, dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1-1:1) to obtain compound **1-10**. MS m/z =612.1 $[M+H]^+$.

Step 10

Compound **1-10** (30 g, 49.05 mmol) was weighed, tetrahydrofuran (300 mL) was added, and lithium trissec-butylborohydride (1 M, 53.96 mL) was added at -60°C. React at -60°C for 1 hour, add 200 mL of water to the system to quench the reaction, extract with ethyl acetate (300 mL*2), combine the

extracted organic phases, wash with 300 mL of saturated brine, dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1-5:1) to obtain compound **1-11**. MS m/z =614.1 $[M+H]^+$.

Step 11

Compounds **1-11** (20 g, 32.59 mmol) were weighed, ethanol (200 mL) was added, and 2-methyl-2-thioisourea sulfate (27.22 g, 97.78 mmol) was added, sodium carbonate (6.91 g, 65.19 mmol) was reacted at 50°C for 13 hours. The reaction solution was concentrated and dried, 40 mL of water was added, extracted with ethyl acetate (50 mL*2), the extracted organic phase was combined, washed with 60 mL of saturated brine, and dried with anhydrous sodium sulfate. The compounds **1-12** were concentrated under reduced pressure by filtration. MS m/z =654.3 $[M+H]^+$.

Step 12

Compounds **1-12** (21 g, 32.13 mmol), DMF (200 mL), N,N-diisopropylethylamine (12.46 g, 96.38 mmol, 16.79 mL), N,N-bis(trifluoromethylsulfonyl)aniline (13.77 g, 38.55 mmol), and reacted at 25°C for 1 hour. Added with 300 mL of water to the system, extracted with ethyl acetate (300 mL*3), washed with water (400 mL*2) and saturated brine (400 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1) to obtain compounds **1-13**. Preparation SFC splitting was performed (chromatographic column: DAICEL CHIRALPAK IG (250 mm*50 mm, 10 μm); mobile phase: [supercritical carbon dioxide-ethanol (0.1% ammonia)]; ethanol (0.1% ammonia water)%: 25%-25%) to obtain compound **1-13B**. Chiral SFC analysis (chromatographic column: ChiralPak IG-3 (100 mm * 4.6 mm, 3 μm); mobile phase: [supercritical carbon dioxide-ethanol (0.05% diethylamine)]; (ethanol (0.05% diethylamine)%)%: 5%-40%), Rt = 3.055 minutes for compound **1-13B**, ee value 99%.

Step 13

Compound **1-13B** (200 mg, 254.53 μmol) and compound **1-14A** (174.74 mg) were added to N, N-dimethylformamide (2 mL), and then N, N-diisopropylethylamine (131.58 mg, 1.02 mmol) was added. The resulting reaction solution was heated to 105°C under nitrogen protection and stirred for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product column chromatography purification (petroleum ether: Ethyl acetate = 5:1) to obtain compounds **1-14**. MS m/z= 906.3 $[M+H]^+$.

Step 14

Compounds **1-14** (120 mg, 132.45 μmol) were dissolved in methylene chloride (2 mL), then metachloroperoxybenzoic acid (29.58 mg, 145.70 μmol, 85% purity) was added, and the reaction solution was stirred and reacted for 2 hours at 20°C under nitrogen protection. The reaction solution

was diluted with 30 mL dichloromethane, then washed with 5 mL saturated sodium bicarbonate solution and 5 mL saturated brine, the organic phase dried, and concentrated under reduced pressure to obtain compounds **1-15**. MS m/z= 922.7 $[M+H]^+$.

Step 15

Sodium tert-butanol (23.97 mg, 249.46 μmol) and compound **1-2** (38.22 mg, 249.46 μmol) were added to tetrahydrofuran (1.5 mL), and the reaction was stirred at 20 °C for 0.5 hours. Then, a solution of compound **1-1**5(115 mg, 124.73 μmol) in tetrahydrofuran (1 mL) was added to the above system, and the reaction was continued to be stirred for 1 hour. Adjust the pH of the reaction solution to 7 by using 0.5M hydrochloric acid. Then, add 20mL of ethyl acetate and 10mL of water, and stir to dissolve. Separate the aqueous layer. Wash the organic phase with 2mL of saturated saline solution. Dry the organic phase with anhydrous sodium sulfate, filter, and concentrate the filtrate under reduced pressure to obtain compound **1-16**. MS m/z= 1011.5 $[M+H]^+$.

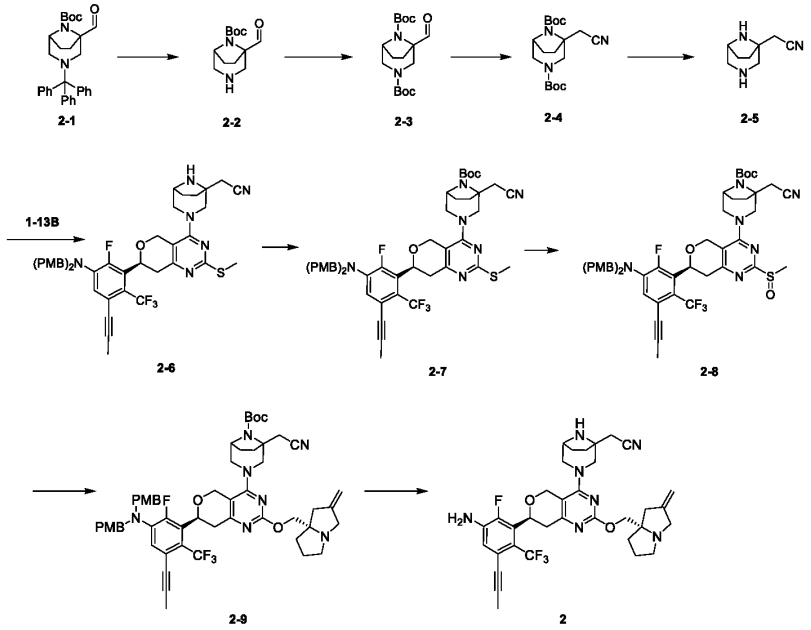
Step 16

Compounds **1-16** (120.00 mg, 118.68 μmol) were dissolved in tetrahydrofuran (2 mL), the resulting solution was cooled to 0 °C, and then lithium tetrahydroaluminum (1 M, 118.68 μL) was added dropwise to the mixture, and the reaction was stirred for 0.5 hours. The reaction solution was carefully quenched with 0.2 mL of water, then 0.5 g of anhydrous sodium sulfate was added and stirred for 2 minutes. Diatomaceous earth was paddled and filtered. The filter cake was rinsed with 20 mL of tetrahydrofuran, the filtrate was collected, and concentrated under reduced pressure to obtain compound **1-17**. MS(ESI)m/z= 983.4 $[M+H]^+$.

Step 17

Compounds **1-17** (120 mg, 122.06 μmol) were added to trifluoroacetic acid (2 mL), and the reaction was stirred and reacted at 20 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was separated by high performance liquid chromatography (chromatographic column: Xtimate C18 150*40mm*5μm; mobile phase: [water (0.05% hydrochloric acid)-acetonitrile]; acetonitrile): 10%-40%, concentrated under reduced pressure to obtain the hydrochloride salt of compound **1**. MS m/z= 643.3$[M+H]^+$.

Example 2



Step 1

Compound **2-1** (2.3 g, 4.77 mmol) was dissolved in dioxane (30 mL), and then hydrochloric acid (1 M, 14.30 mL) was added. The reaction solution was stirred and reacted for 1 hour under nitrogen protection at 20 °C. The reaction solution was concentrated under reduced pressure. 20 mL of water and 50 mL of ethyl acetate were added to the residue and stirred to make it fully dissolved. The aqueous phase was separated. The organic phase was washed with 10 mL of 0.5 M hydrochloric acid. The aqueous phase was combined, pH = 10 was adjusted with 20% sodium carbonate solution, then extracted with dichloromethane (20 mL x 2), the organic phase was combined, and concentrated under reduced pressure to obtain compound **2-2**.

Step 2

For the compound **2-2** (1.2 g, 4.77 mmol), it was added 20 mL of dichloromethane, then Boc_2O (2.08 g, 9.53 mmol) was added, and the reaction was stirred at 20 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product column chromatography purification (petroleum ether: Ethyl acetate = 5:1) obtained compound **2-3**. ^{1}HNMR (400MHz, $CDCl_3$) δ: 9.55 - 9.47（m, 1H）, 4.40-4.00 (m, 2H), 3.95 - 3.55 (m, 1H), 3.30 - 2.90 (m, 2H), 2.25 - 1.91 (m, 2H), 1.78 (s, 2H), 1.47 (s, 18H)。

Step 3

Potassium tert-butanol (830.68 mg, 7.40 mmol) was added to glycol dimethyl ether (25 mL), the resulting mixture was cooled to -78°C, then added p-methylbenzene sulfonyl methyl isonitrile (794.91 mg, 4.07 mmol), after addition, stirred for 30 minutes, and then added compound **2-3** (1.26

g, 3.70 mmol) dropwise to the mixture (25 mL), after dropping, stirred for 30 minutes, removed from the cooling bath, increased to room temperature for 20 minutes, finally added methanol 40 mL, and the resulting final reaction solution was heated to 90°C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product column chromatography purification (petroleum ether: Ethyl acetate = 3:1) obtained compound **2-4**. ^{1}HNMR（400MHz, $CDCl_3$）δ: 4.22 (s, 1H), 3.65 - 3.55 (m, 2H), 3.30-2.62 (m, 4H), 1.99 - 1.89 (m, 2H), 1.65 - 1.30 (m, 20H).

Step 4

Compound **2-4** (375 mg, 1.07 mmol) was dissolved in dichloromethane (2 mL), and then trifluoroacetic acid (1.22 g, 10.67 mmol) was added. The resulting reaction solution was stirred and reacted for 1 hour at 20 °C under nitrogen protection. The reaction solution was concentrated under reduced pressure, 20 mL of ethyl acetate was added to the residue, and then 1 mL of hydrogen chloride/ethyl acetate solution (4M) was added to it, and concentrated under reduced pressure to obtain the hydrochloride salt of compound **2-5**.

Step 5

Compound **1-13B** (350 mg, 445.44 μmol) and the hydrochloride salt of compound **2-5** (299.51 mg) were added to N,N-dimethylformamide (3 mL), and then N,N-diisopropylethylamine (460.56 mg, 3.56 mmol) was added. The resulting reaction solution was heated to 105°C under nitrogen protection and stirred for 1 hour. The reaction solution was concentrated under reduced pressure to give the crude product, which was dissolved in 50 mL of ethyl acetate, then washed with saturated brine (10 mL x 2), dried in an organic phase, and concentrated under reduced pressure to obtain compounds **2-6**. MS m/z=787.2$[M+H]^+$.

Step 6

Compound **2-6** (368 mg, 467.67 μmol) and N,N-diisopropylethylamine (120.89 mg, 935.34 μmol) were added to dichloromethane (3 mL), and then Boc_2O (153.10 mg, 701.51 μmol) was added, and the reaction solution was stirred for 3 hours under nitrogen protection at 20°C. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product column chromatography purification (petroleum ether: Ethyl acetate = 3:1) obtained compound **2-7**. MS m/z=887.4$[M+H]^+$.

Step 7

Compound **2-7** (220 mg, 248.03 μmol) was dissolved in methylene chloride (2 mL), and then metachloroperoxybenzoic acid (50.35 mg, 248.03 μmol, 85% purity) was added. The reaction solution was obtained under nitrogen protection and stirred and reacted at 20 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain compounds **2-8**. MS m/z=903.6$[M+H]^+$.

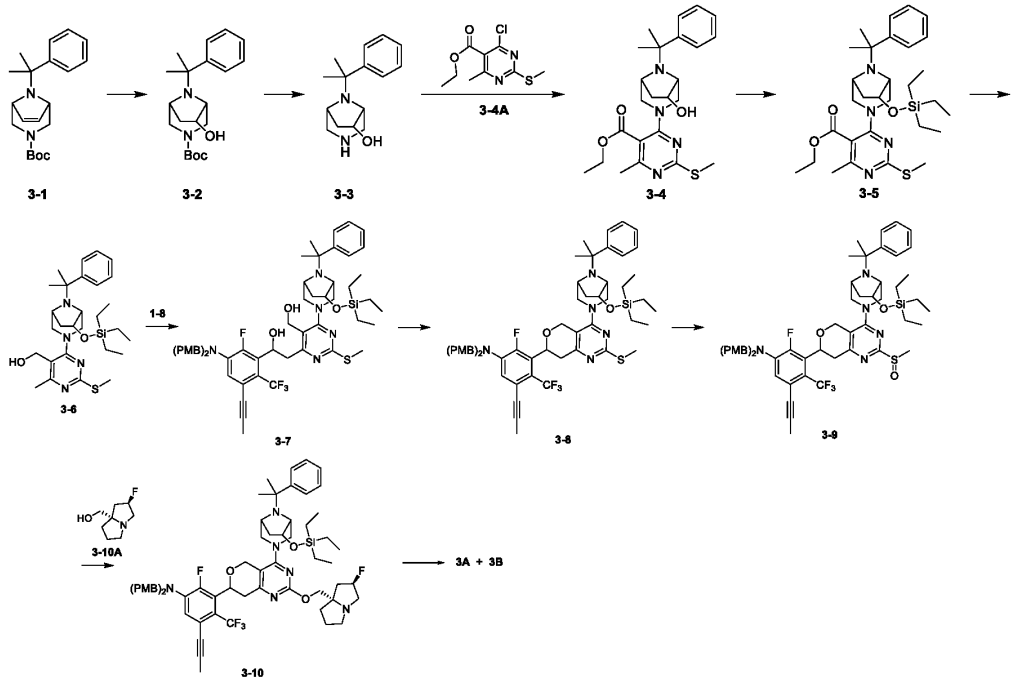
Step 8

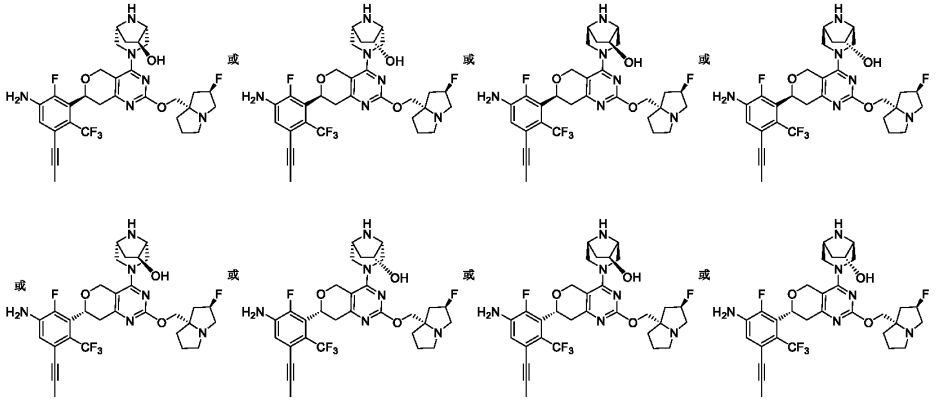
Compound **1-2** (75.68 mg, 493.91 μmol) was dissolved in THF (2 mL), then sodium tert-butanol (47.47 mg, 493.91 μmol) was added, and the reaction was stirred at 20 °C for 1 hour under nitrogen protection, and then a solution of compound **2-8** (223 mg, 246.96 μmol) in tetrahydrofuran (1 mL) was added to the solution, and after addition, the reaction was stirred at 20 °C for 0.5 hours. The reaction solution was dissolved in 10 mL of ethyl acetate, then washed with 5 mL of saturated brine, the organic phase dried, then filtered, and the filtrate was concentrated under reduced pressure to obtain compounds **2-9**. MS m/z=992.5[M+H]$^+$.

Step 9

Trifluoroacetic acid (2 mL) was added to compounds **2-9** (214 mg, 215.70 μmol), and the resulting reaction solution was stirred at 20 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared by high performance liquid chromatography separation (chromatographic column: Xtimate C18 150 * 40 mm * 5 μm; mobile phase: [water (0.05% hydrochloric acid)-acetonitrile]; acetonitrile): 10%-40%), concentrated under reduced pressure to obtain the hydrochloride salt of compound **2**. MS m/z=652.2[M+H]$^+$.

Example 3





3A或3B(单一化合物或者混合物)

Step 1

Borane tetrahydrofuran solution (1 M, 21 mL) was added slowly dropwise to anhydrous THF (20 mL) solution of compound 3-**1** (1.7 g, 5.18 mmol) under nitrogen protection at 0 °C, and then stirred at 25 °C for 12 hours. 5% NaOH solution (26.31 mmol, 21 mL) was added dropwise at 0°C, followed by di-oxygen water (4.88 g, 43.04 mmol, 4.14 mL, 30% purity) was added dropwise. React at 25 °C for 2 hours. The solution was quenched by slowly adding 50 mL of saturated sodium sulphite solution to the reaction solution and extracted with 50 mL of ethyl acetate. The organic phase was washed with 50 mL of salt, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was chromatographically separated with a thin layer of preparation (petroleum ether: Ethyl acetate = 3:1) to obtain compound **3-2**. MS m/z = 347.2$[M+H]^+$.

Step 2

To anhydrous dioxane (10 mL) solution of compound **3-2** (1 g, 2.89 mmol), it was added hydrochloric acid/dioxane solution (4 M, 10 mL), and the solution was reacted at 20 degrees for 0.5 hours. The reaction solution was concentrated under reduced pressure to obtain the hydrochloride salt of compound **3-3**.

Step 3

Compound **3-4A** (750 mg, 3.04 mmol) was dissolved in anhydrous DCM (10 mL), followed by addition of triethylamine (584 mg, 5.77 mmol) and hydrochloride of compound **3-3** (921 mg) and reacted at 20 °C for 1 hour. A dichloromethane solution of compound **3-4** was obtained and directly injected into the next step reaction. MS m/z = 457.2 $[M+1]^+$.

Step 4

For dichloromethane solution (10 mL) of compound **3-4** obtained in step 3, it was added with triethylchlorosilane (871 mg, 5.78 mmol) and imidazole (590 mg, 8.67 mmol), respectively. React d at 25°C for 12 hours. The reaction solution was diluted with 10 mL of water and extracted with 10

mL of dichloromethane. The organic phase was washed with 10 mL of salt, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was separated by column chromatography (petroleum ether: Ethyl acetate = 50:1) to obtain compound **3-5**. MS m/z = 571.3[M+1]$^+$.

Step 5

THF (20 mL) solution of compound **3-5** (1.43 g, 2.50 mmol), and lithium hydride tetrahydrofuran solution (2.5 M, 2.00 mL) was slowly added at 0 °C. The solution was reacted at 25°C for 5 hours, and ethyl acetate (10 mL) was added dropwise to the reaction solution to quench the reaction, and the resulting suspension was filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 20:1) to obtain compound **3-6**. MS m/z = 529.3[M+1]$^+$.

Step 6

Compound tetramethylpiperidine (460 mg, 3.26 mmol) was dissolved in anhydrous tetrahydrofuran (1.0 mL), cooled to -40 °C under nitrogen protection, and then n-butyllithium (2.5 M 1.3 mL) was added dropwise thereto. The reaction was stirred for 0.5 hours, compound **3-6** (430 mg, 813 μmol) was dissolved in anhydrous tetrahydrofuran (0.5 mL), and added dropwise to the reaction vessel at -60°C. After dripping, the reaction was stirred for 0.5 hours. Finally, an anhydrous tetrahydrofuran 0.5 mL solution of compound **1-8** (486 mg, 1.00 mmol) was added to the reaction under -60 °C and then heated to 20 °C for 2.5 hours. Add 20 mL of water to quench reaction, and then extract with ethyl acetate (20 mL). The organic phase was washed with 20 mL of salt, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 5:1), and then a thin layer of chromatographic separation (petroleum ether: Ethyl acetate = 3:1) obtained compound **3-7**. MS m/z = 1014.5[M+H]$^+$.

Step 7

Compounds **3-7** (70 mg, 69.0 μmol) were dissolved in anhydrous toluene (1.5 mL), cyanomethylenetrin-butylphosphine (150 mg, 621.50 μmol) was added, and the reaction was stirred at 110°C for 12 hours after nitrogen replacement. The reaction solution was cooled and concentrated under reduced pressure to obtain the crude product. Preparation thin layer chromatography purification of crude product (petroleum ether: Ethyl acetate = 5:1) obtained compounds **3-8**. MS m/z = 996.5[M+H]$^+$.

Step 8

Compound **3-8** (22.5 mg, 22.58 μmol) was dissolved in anhydrous dichloromethane (0.5 mL), 5 mg, 24.63 μmol, 85% purity) was added, and the reaction was stirred at 25°C for 12 hours. Add 4 mL of

saturated sodium sulfite solution to the reaction solution to quench the reaction and extract with dichloromethane (20 mL*3). The organic phase was washed with 20 mL of brine, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. Preparation thin layer chromatography purification of crude product (petroleum ether: Ethyl acetate = 5:1) obtained compounds **3-9**. MS m/z = 1012.6$[M+H]^+$.

Step 9

Compound **3-9** (19 mg, 18.8 μmol) was dissolved in anhydrous toluene (0.5 mL), sodium tert-butoxide (7.22 mg, 75.1 μmol), 4Å molecular sieve (10 mg) and compound **3-10A** (12 mg, 75.08 μmol) were added, and the solution was stirred at 100 °C for 12 hours. The reaction solution was cooled, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. Crude product preparation thin layer chromatographic purification (ethyl acetate:methanol = 10:1) to obtain compound **3-10**. MS m/z = 1107.7$[M+H]^+$.

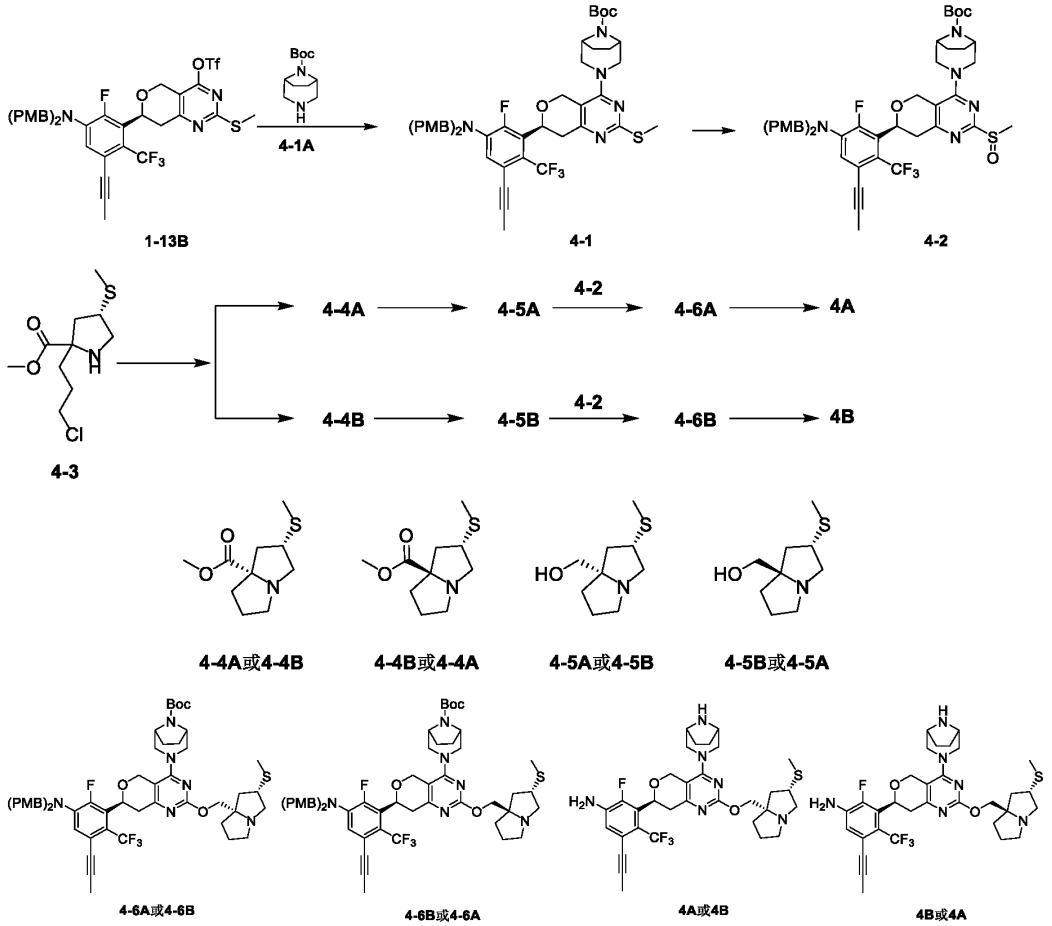
Step 10

Compounds **3-10** (17 mg, 15.35 μmol) were dissolved in trifluoroacetic acid (5 mL) and reacted at 20°C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 18%-48% to obtain the trifluoroacetate salt of compound **3A** and the trifluoroacetate salt of **3B**.

Trifluoroacetate of compound **3A** (single compound or mixture), MS m/z = 635.3$[M+H]^+$. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.94 (d, *J* = 8.50 Hz, 1 H), 5.71 - 5.50 (m, 1 H), 5.17 (br dd, *J* = 10.94, 4.06 Hz, 1 H), 4.80 (br d, *J* = 13.63 Hz, 2 H), 4.62 - 4.48 (m, 3 H), 4.17 - 3.73 (m, 7 H), 3.54 - 3.36 (m, 3 H), 3.31 - 3.25 (m, 1 H), 2.93 (br dd, *J* = 18.01, 3.75 Hz, 1 H), 2.77 - 2.48 (m, 3 H), 2.46 - 2.28 (m, 3 H), 2.26 - 2.12 (m, 1 H), 2.04 (s, 3 H), 1.96 (dd, *J* = 14.01, 4.13 Hz, 1 H)。

Trifluoroacetate of compound **3B** (single compound or mixture), MS m/z = 635.2$[M+H]^+$. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.93 (d, *J* = 8.50 Hz, 1 H), 5.69 - 5.49 (m, 1 H), 5.30 (d, *J* = 13.88 Hz, 1 H), 5.18 (br dd, *J* = 11.19, 3.56 Hz, 1 H), 4.87 - 4.78 (m, 2 H), 4.69 - 4.50 (m, 3 H), 4.29 (br d, *J* = 13.26 Hz, 1 H), 4.20 - 3.87 (m, 6 H), 3.63 (br d, *J* = 14.51 Hz, 1 H), 3.53 - 3.42 (m, 1 H), 3.35 (br s, 1 H), 2.93 (br dd, *J* = 17.70, 3.56 Hz, 1 H), 2.77 - 2.51 (m, 3 H), 2.47 - 2.28 (m, 3 H), 2.26 - 2.12 (m, 1 H), 2.04 (s, 3 H), 1.83 (dd, *J* = 13.88, 4.25 Hz, 1 H).

Example 4



Step 1

Compound **1-13B** (240 mg, 305.44 μmol) and compound **4-1A** (97.26 mg, 458.16 μmol) were dissolved in DMF (5 mL), DIPEA (916.33 μmol, 159.61 μL) was added, and then stirred at 100°C for 1 hour. Extract with 30 mL of ethyl acetate, wash the organic phase with 50 mL of salt, dry with anhydrous sodium sulfate, filter, and concentrate the filtrate under reduced pressure to obtain the crude product. The crude product was chromatographically separated with a thin layer of preparation (petroleum ether: Ethyl acetate = 5:1) to obtain compound **4-1**. MS m/z = 848.5$[M+H]^+$.

Step 2

Compound **4-1** (200 mg, 235.86 μmol) was dissolved in dichloromethane (5 mL), metachloroperoxybenzoic acid (40.70 mg, 235.86 μmol, 85% purity) was added, and stirred at 25°C for 1 hour. Add 5 mL of dichloromethane for extraction, wash with 10 mL of saturated sodium bicarbonate, dry with anhydrous sodium sulfate, filter, and concentrate the filtrate under reduced pressure to obtain the crude product. The crude product was chromatographically separated with a thin layer of preparation (dichloromethane: methanol = 10:1) to give compound **4-2**. MS m/z =

864.3[M+H]$^+$.

Step 3

Compounds **4-3** (610 mg, hydrochloride) were dissolved in acetonitrile (10 mL), to which potassium carbonate (1.46 g, 10.6 mmol) and potassium iodide (35.1 mg, 212 μmol) were added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 5: 1), and then separated by a thin layer of chromatography (petroleum ether: ethyl acetate = 1:1) to give compound **4-4A** and compound **4-4B**, wherein compound **4-4A** (petroleum ether: ethyl acetate = 1: 1, R_f = 0.21), MS m/z = 216.0[M+1]$^+$, compound **4-4B** (petroleum ether: ethyl acetate = 1: 1, R_f = 0.12), MS m/z = 216.1[M+1]$^+$.

Compound **4-4A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.75 (s, 3H), 3.54 (dd, *J* = 6.5, 9.0 Hz, 1H), 3.33 (tt, *J* = 6.4, 10.6 Hz, 1H), 3.13 (td, *J* = 6.4, 10.8 Hz, 1H), 2.86 - 2.75 (m, 2H), 2.52 (t, *J* = 9.6 Hz, 1H), 2.30 - 2.18 (m, 1H), 2.15 (s, 3H), 1.99 - 1.81 (m, 3H), 1.61 (dd, *J* = 11.3, 12.6 Hz, 1H); Compound**4-4B**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.67 (s, 3H), 3.28 - 3.08 (m, 2H), 3.06 - 2.92 (m, 2H), 2.56 (td, *J* = 7.4, 9.5 Hz, 1H), 2.37 - 2.17 (m, 2H), 2.09 (dd, *J* = 6.9, 13.2 Hz, 1H), 2.04 (s, 3H), 1.79 - 1.69 (m, 2H), 1.67 - 1.56 (m, 1H)。

Step 4

Compound **4-4A** (102 mg, 474 μmol) was dissolved in THF (5.0 mL), lithium tetrahydroaluminum (2.5 M, 0.3 mL) was added dropwise at 0 °C, and the reaction solution was heated to 25 °C for 1 hour. Add 0.03 mL of water, 0.03 mL of 15% aqueous sodium hydroxide solution and 0.1 mL of water dropwise at 0°C, and stir for 0.5 hours. The mixture was filtered, the filter cake was washed with 10 mL of ethyl acetate, and the filtrate was concentrated under reduced pressure to give compound **4-5A**, MS m/z = 188.1 [M+1]$^+$.

Step 5

Compound **4-2** (120 mg, 139 μmol), compound **4-5A** (89 mg, 475 μmol), 4Å molecular sieve (120 mg) and sodium tert-butanol (80 mg, 832 μmol) were added to toluene (15 mL), and the temperature was increased to 100 °C for 6 hours. The reaction solution was filtered, the filter cake was washed with 10 mL of ethyl acetate, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by preparing a thin layer of chromatographic separation (dichloromethane: methanol = 10: 1) to obtain compound **4-6A**, MS m/z = 987.4[M+1]$^+$.

Step 6

Compound **4-6A** (81 mg, 82.0 μmol) was dissolved in dichloromethane (10.0 mL), to which trifluoroacetic acid (3.07 g, 26.9 mmol, 2 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain the crude

product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 15%-45%, and purified to obtain the trifluoroacetate salt of compound **4A**. MS m/z =647.3[M+1]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, J = 8.5 Hz, 1H), 5.21 (br dd, J = 3.9, 11.1 Hz, 1H), 4.79 - 4.49 (m, 4H), 4.47 - 4.32 (m, 1H), 4.24 - 4.02 (m, 3H), 3.86 (br d, J = 13.9 Hz, 1H), 3.76 - 3.65 (m, 2H), 3.65 - 3.55 (m, 1H), 3.54 - 3.46 (m, 1H), 3.41 - 3.35 (m, 1H), 3.20 - 3.08 (m, 1H), 3.01 - 2.89 (m, 1H), 2.71 (br dd, J = 6.5, 13.4 Hz, 1H), 2.41 - 2.19 (m, 8H), 2.19 - 1.90 (m, 8H)。

Step 7

Compound **4-4B** (51 mg, 237 μmol) was dissolved in THF (3.0 mL), lithium tetrahydroaluminum (2.5 M, 0.15 mL) was added dropwise at 0°C, and the reaction solution was heated to 25°C for 1 hour. Add 0.02 mL of water, 0.02 mL of 15% aqueous NaOH solution and 0.06 mL of water dropwise at 0 °C, and stir for 0.5 hours. The mixture was filtered, the filter cake was washed with 10 mL of ethyl acetate, and the filtrate was concentrated under reduced pressure to obtain compound **4-5B**, MS m/z = 188.2 [M+1]$^+$.

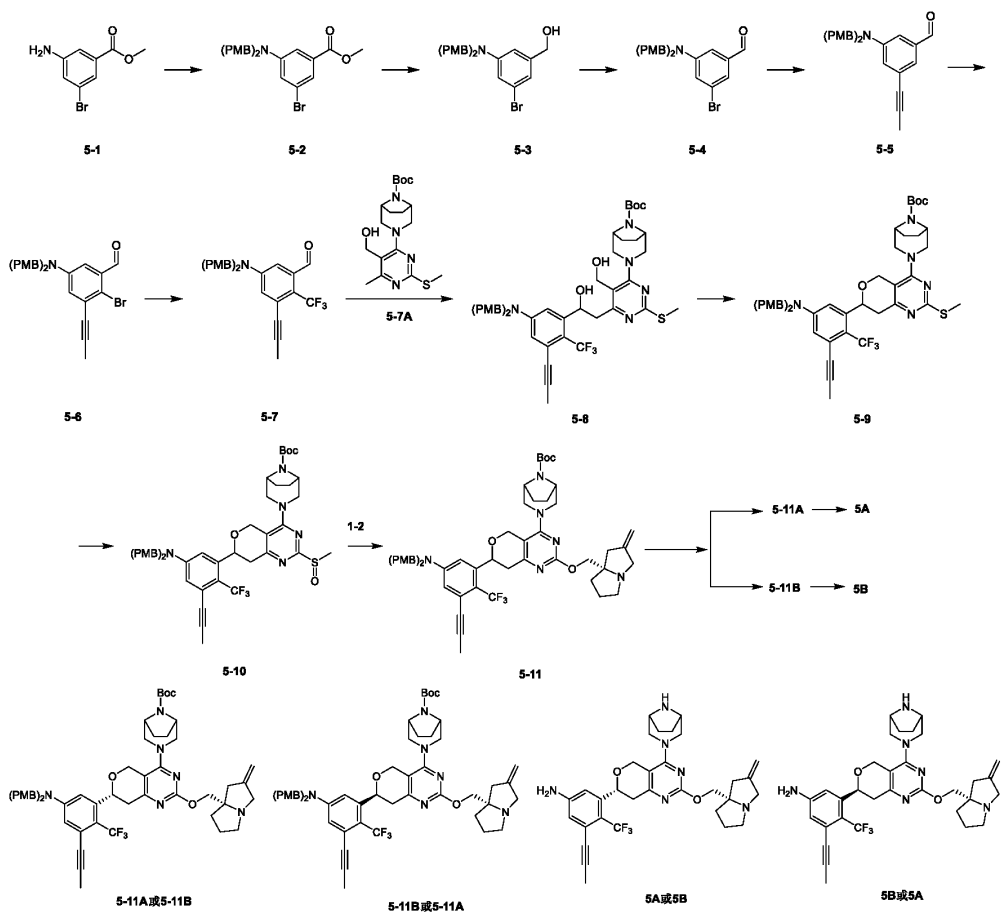
Step 8

Compound **4-2** (100 mg, 116 μmol), compound **4-5B** (41 mg, 219 μmol), 4Å molecular sieve (70 mg) and sodium tert-butanol (80 mg, 832 μmol) were added to toluene (15 mL), and the temperature was increased to 100 °C for 6 hours. The reaction solution was filtered, the filter cake was washed with 10 mL of ethyl acetate, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by preparing a thin layer of chromatographic separation (dichloromethane: methanol = 20: 1) to obtain compound **4-6B**, MS m/z = 987.4[M+1]$^+$.

Step 9

Compounds **4-6B** (70 mg, 70.9 μmol) were dissolved in dichloromethane (10.0 mL), to which trifluoroacetic acid (3.07 g, 26.9 mmol, 2 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 15%-45%, and purified to obtain the trifluoroacetate salt of compound **4B**. MS m/z =647.3[M+1]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, J = 8.5 Hz, 1H), 5.21 (br dd, J = 4.1, 10.6 Hz, 1H), 4.78 - 4.64 (m, 4H), 4.54 (br d, J = 11.8 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.21 - 4.11 (m, 2H), 3.88 - 3.54 (m, 6H), 3.40 - 3.34 (m, 2H), 2.96 (br dd, J = 4.0, 17.9 Hz, 1H), 2.55 - 2.37 (m, 2H), 2.36 - 1.89 (m, 14H).

Example 5



Step 1

Compound **5-1** (10.0 g, 43.5 mmol) was dissolved in DMF (4 mL), then potassium carbonate (15.0 g, 109 mmol) and p-methoxybenzyl chloride (16.3 g, 104 mmol, 14.2 mL) were added and reacted at 80 °C for 12 hours. After the reaction solution was reduced to room temperature, 200 mL ethyl acetate was added to the reaction solution, washed with 200 mL water and 100 mL saturated salt water, anhydrous sodium sulfate was dried, filtered, and reduced pressure was obtained The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 30:1) to obtain compound **5-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 (t, *J* = 1.31 Hz, 1H), 7.41 (dd, *J* = 2.38, 1.13 Hz, 1H), 7.13 (d, *J* = 8.50 Hz, 4H), 7.06 - 7.02 (m, 1H), 6.92 - 6.83 (m, 4H), 4.56 (s, 4 H), 3.86 (s, 3 H) 3.81 (s, 6 H).

Step 2

Compound **5-2** (17.5 g, 37.2 mmol) was dissolved in anhydrous THF (200 mL), then $LiAlH_4$ (2.5 M, 30 mL) was added at 0 °C, and then reacted at 25 °C for 1 hour. The temperature of the reaction solution was reduced to room temperature, and 2.85 mL of H_2O, 2.85 mL of 15% NaOH aqueous

solution and 8.6 mL of H_2O were added dropwise slowly under nitrogen flow. The solid produced was filtered and the filtrate was concentrated under reduced pressure to obtain compound **5-3**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.03 (d, J = 8.63 Hz, 4H), 6.82 - 6.67 (m, 6H), 6.57 (s, 1H), 4.44 (s, 6H), 3.71 (s, 6H).

Step 3

Compound **5-3** (15.0 g, 33.9 mmol) was dissolved in THF (150 mL), nitrogen replacement was performed for three times, MnO_2 (60.0 g, 690 mmol) was added, and the reaction solution was cooled at 75°C for 12 hours, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 20:1) to obtain compound **5-4**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.79 (s, 1H), 7.16 - 7.09 (m, 6H), 6.92 - 6.86 (m, 5H), 4.59 (s, 4H), 3.81 (s, 6H).

Step 4

Compounds **5-4** (7.20 g, 16.4 mmol), 1-propynyltri-N-butyltin (5.38 g, 16.4 mmol), dichlorobis[di-tert-butyl-(4-dimethylaminophenyl)phosphine]palladium(II)(57.9 mg, 81.8 μmol) were dissolved in anhydrous toluene (170 mL), nitrogen was replaced three times, and then reacted at 110 °C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain compound **5-5**. MS m/z = 400.3$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.82 (s, 1H), 7.21 (s, 1H), 7.18 - 7.15 (m, 1H), 7.12 (d, J = 8.63 Hz, 4H), 7.03 - 7.01 (m, 1H), 6.87 (d, J = 8.63 Hz, 4H), 4.58 (s, 4H), 3.81 (s, 6H), 2.02 (s, 3H).

Step 5

Compounds **5-5** (4.60 g, 11.5 mmol) were dissolved in anhydrous DMF (50 mL), NBS (2.25 g, 12.7 mmol) was added, and reacted at room temperature for 0.5 hours. Water (150 mL) was added to the organic phase, extracted with ethyl acetate (50 mL) for 3 times, the organic phase washed for 3 times with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain compounds **5-6**. MS m/z = 478.2$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.31 (s, 1H), 7.24 (d, J = 3.38 Hz, 1H), 7.10 (d, J = 8.63 Hz, 4H), 7.05 (d, J = 3.38 Hz, 1H), 6.89 - 6.83 (m, 4H), 4.55 (s, 4H), 3.80 (s, 6H), 2.09 (s, 3H).

Step 6

Compounds **5-6** (5.30 g, 11.1 mmol), methylene iodide (4.22 g, 22.2 mmol), 2,2-difluoro-2-fluorosulfonylacetate (8.09 g, 42.1 mmol) were dissolved in DMF (50 mL), nitrogen was replaced three times, and the solution was reacted at 110 °C for 2.5 hours. The reaction solution was cooled,

filtered with diatomaceous earth, water (150 mL) was added to the organic phase, and extracted 3 times with EA (150 mL). The organic phase was washed three times with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 20:1) to obtain compounds **5-7**. MS m/z = 468.2$[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.30 (q, *J* = 2.71 Hz, 1H), 7.25 (d, *J* = 2.75 Hz, 1H), 7.10 (d, *J* = 8.63 Hz, 4H), 7.00 (d, *J* = 2.88 Hz, 1H), 6.90 - 6.85 (m, 4H), 4.60 (s, 4H), 3.81 (s, 6H), 2.05 (d, *J* = 4.13 Hz, 3H).

Step 7

TMP (2.45 g, 17.4 mmol, 2.94 mL) was dissolved in THF (20 mL), nitrogen was replaced three times, the temperature was reduced to -40°C, n-BuLi (2.5 M, 6.71 mL) was added slowly dropwise, after dropping, reacted at -40°C for 30 minutes, the reaction system was cooled to -60°C, **5-7A**(2.20 g, 5.78 mmol) of THF (20 mL) solution was added slowly dropwise to the above reaction solution, and reacted at -40°C for 15 minutes, compound **5-7**(3.94 g, 6.94 mmol) was added into the above reaction solution in batches, and the reacted at room temperature for 2 hours. The reaction solution was quenched with saturated aqueous ammonium chloride (100 mL), and extracted twice with ethyl acetate (100 mL). The organic phase was washed twice with saturated brine (100 mL), dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 2:1) to obtain compound **5-8**, MS m/z = 848.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.15 - 6.99 (m, 5H), 6.79 (d, *J* = 8.63 Hz, 4H), 6.75 (br d, *J* = 2.38 Hz, 1H), 5.39 (br d, *J* = 8.63 Hz, 1H), 4.84 - 4.40 (m, 5H), 4.38 - 4.12 (m, 5H), 3.72 (s, 6H), 3.42 - 3.11 (m, 2H), 3.06 - 2.86 (m, 1H), 2.70 - 2.51 (m, 1H), 2.40 (s, 3H), 2.36 - 2.23 (m, 1H), 1.94 (s, 2H), 1.85 – 1.74 (m, 3H), 1.66 (br d, *J* = 9.13 Hz, 1H), 1.42 (s, 9H)。

Step 8

Compounds **5-8** (324 mg, 390 μmol) were dissolved in anhydrous toluene (23 mL), cyanomethylene tributyl phosphate (1.30 g, 5.40 mmol) was added, and nitrogen was replaced for three times and reacted at 110 °C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. Crude product was purified by column chromatography (petroleum ether: Ethyl acetate = 10:1) and preparation of high performance liquid chromatography separation (chromatographic column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.05% hydrochloric acid)-acetonitrile]; acetonitrile: 55%-85%); concentrated under reduced pressure to obtain the hydrochloride salt of compound **5-9**. MS m/z = 830.5$[M+H]^+$.

Step 9

Compound **5-9** (324 mg, hydrochloride) was dissolved in anhydrous dichloromethane (3 mL), metachloroperoxybenzoic acid (83.2 mg, 410 μmol, 85% purity) was added, and then reacted at room temperature for 0.5 hours. The reaction solution was concentrated under reduced pressure and sodium bicarbonate (10 mL), sodium sulfite (10 mL) was quenched, extracted twice with DCM (50 mL), washed with 50 mL of saturated salt, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to obtain compound **5-10**. MS m/z = 846.5$[M+H]^+$.

Step 10

Compound **5-10** (280 mg, 331 μmol) was dissolved in anhydrous toluene (20 mL), 4Å molecular sieve (150 mg, 2.34 mmol), compound **1-2** (203 mg, 1.32 mmol*), sodium* tert-butoxide (127 mg, 1.32 mmol) was added, and then reacted at 100 °C for 12 hours. The reaction solution was filtered and concentrated under reduced pressure to obtain the crude product. Crude product was purified by column chromatography (dichloromethane: methanol = 20:1) and prepared for high performance liquid chromatography separation (chromatographic column: Phenomenex luna C18 150*30mm* 10μm; mobile phase: [water (0.225% formic acid)-acetonitrile]; (acetonitrile): 48%-78%) and concentrated under reduced pressure to obtain the formate salt of compound **5-11**. MS m/z = 935.7$[M+H]^+$. The SFC separation was then prepared (chiral column: DAICEL CHIRALCEL OD (250 mm*30 mm, 10 um); mobile phase: [supercritical carbon dioxide-acetonitrile/isopropanol (0.1% ammonia water)]; acetonitrile/isopropanol (0.1% ammonia water): 45%-45%, and compound **5-11A** and compound **5-11B** were obtained after concentration under reduced pressure. After analysis, SFC (chiral column: DAICEL CHIRALCEL OD-3 (50 mm*4.6 mm, 3 μm; mobile phase: [supercritical carbon dioxide-methanol (0.05% diethylamine)]; methanol (0.05% diethylamine)%: 40%, compound **5-11A**, Rt=0.657 min, ee value 99%; MS m/z = 935.6$[M+H]^+$; compound **5-11B**, Rt=1.848 min, ee value 99% MS m/z = 935.5$[M+H]^+$.

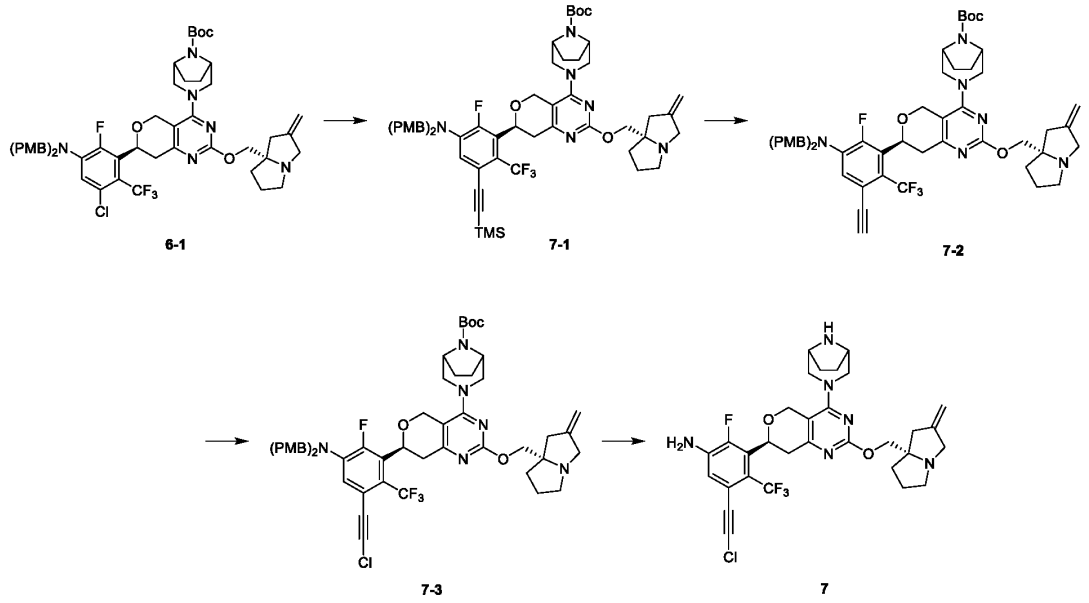
Step 11

Compound **5-11A** (105 mg, 112 μmol) was dissolved in TFA (1 mL) and then reacted at 50 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product, and the crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid-acetonitrile]; acetonitrile: 12%-42%). After lyophilization, the trifluoroacetate of compound **5A** was obtained. MS m/z = 595.4$[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.96 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 5.34 - 5.28 (m, 2H), 5.11 (dd, J = 2.8, 10.8 Hz, 1H), 4.99 - 4.92 (m, 1H), 4.82 - 4.75 (m, 1H), 4.57 (d, J = 1.6 Hz, 2H), 4.44 - 4.30 (m, 2H), 4.21 - 4.11 (m, 2H), 3.96 - 3.83 (m, 2H), 3.81 - 3.66 (m, 2H), 3.33 (br s, 1H), 3.24 (td, J = 7.2, 11.6 Hz, 1H), 3.05 (br s, 1H), 3.03 – 2.98 (m, 1H), 2.87 - 2.74 (m, 2H), 2.41 - 2.32 (m, 1H), 2.30 - 2.19 (m, 2H), 2.18 - 2.05 (m, 4H), 2.05 -

1.93 (m, 4H).

Compounds **5-11B** (110 mg, 118 μmol) were dissolved in TFA (1 mL) and then reacted at 50 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid-acetonitrile]; acetonitrile: 12%-42%, and after lyophilization, the trifluoroacetate salt of compound **5B** was obtained. MS m/z = 595.4[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.97 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 5.30 (br d, *J* = 8.0 Hz, 2H), 5.11 (br dd, *J* = 10.8, 2.8 Hz, 1H), 4.98 - 4.94 (m, 1H), 4.84 - 4.77 (m, 1H), 4.66 - 4.55 (m, 2H), 4.46 (br d, *J* = 14.0 Hz, 1H), 4.34 (br d, *J* = 14.0 Hz, 1H), 4.17 (br d, *J* = 16.0 Hz, 2H), 3.96 - 3.85 (m, 2H), 3.82 - 3.68 (m, 2H), 3.37 (br d, *J* = 14.0 Hz, 1H), 3.23 (td, *J* = 7.2, 11.6 Hz, 1H), 3.03 (br d, *J* = 16.4 Hz, 2H), 2.89 - 2.75 (m, 2H), 2.42 - 2.33 (m, 1H), 2.28 - 2.20 (m, 2H), 2.20 - 2.09 (m, 4H), 2.06 – 1.93 (m, 4H).

Example 7



Step 1

Compound **7-1** (1.20 g, 1.26 mmol) was dissolved in anhydrous toluene (12.0 mL), followed by the addition of tributyl(trimethylsilylethynyl)tin (2.94 g, 7.58 mmol) and dichlorobis[di-tert-butyl-(4-dimethylaminophenyl)phosphine]palladium(II) (537 mg, 758 μmol). The reaction was performed at 110 °C for 20 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 2:1) to obtain compounds **7-1**. MS m/z =1011.6[M+1]$^+$.

Step 2

Compound **7-2** (1.00 g, 989 μmol) was dissolved in anhydrous tetrahydrofuran (10.0 mL), and then tetrabutylammonium fluoride (1 M, 989 μL) was added. React at 25 °C for 4 hours. 30.0 mL of water was added to the reaction solution, extracted with ethyl acetate (150 mL), dried with the organic phase, and concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain compounds **7-2**. MS m/z =939.6$[M+1]^+$.

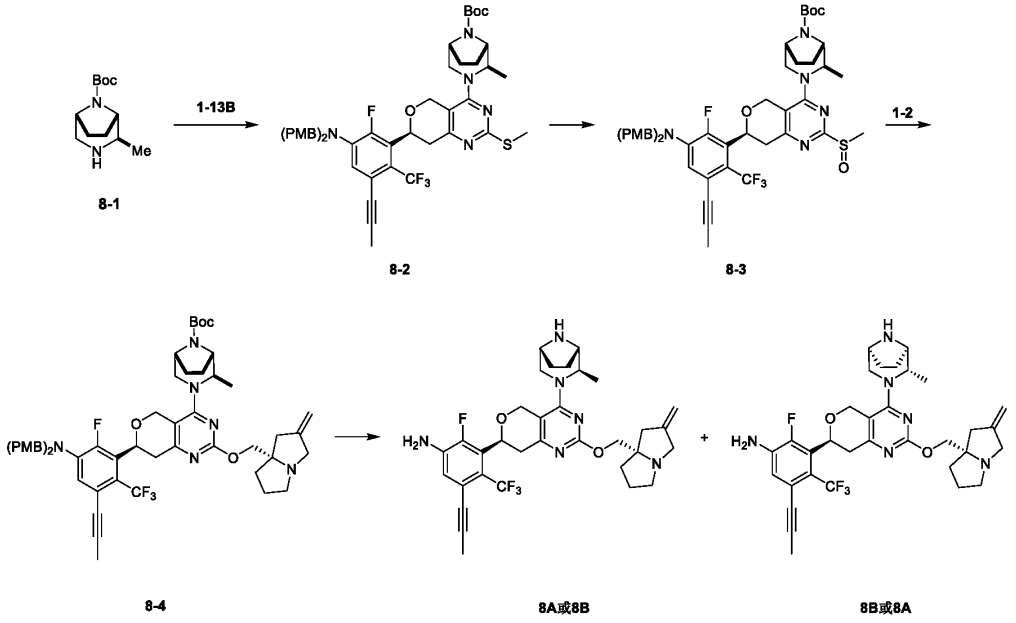
Step 3

Compound **7-2** (310 mg, 330.12 μmol) was dissolved in anhydrous acetone (5 mL), followed by addition of $AgNO_3$ (350 mg, 2.06 mmol), NCS (220.41 mg, 1.65 mmol). At 25 °C Reaction for 10 hours。 The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was purified by preparing a thin layer of chromatographic separation (dichloromethane: methanol = 10:1) to obtain compound **7-3**. MS m/z =973.4$[M+1]^+$.

Step 4

Compound **7-3** (12.0 mg, 12.3 μmol) was dissolved in dichloromethane (1 mL), trifluoroacetic acid (153 mg, 1.35 mmol, 0.1 mL) was added, and the solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 18%-48%. After lyophilization, the trifluoroacetate of compound **7** was obtained. MS m/z =633.2$[M+1]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.00 (d, J = 8.5 Hz, 1H), 5.33 – 5.30 (m, 2H), 5.21 – 5.18 (m, 1H), 4.85 (s, 4H), 4.76 – 4.71 (m, 1H), 4.54 (s, 2H), 4.35 – 4.30 (m, 2H), 4.17 – 4.12 (m, 2H), 3.93 (d, J = 14.0 Hz, 1H), 3.86 – 3.70 (m, 2H), 3.68 – 3.64 (m, 1H), 3.07 - 2.88 (m, 2H), 2.82 – 2.73 (m, 1H), 2.37 – 2.29 (m, 1H), 2.28 – 2.18 (m, 2H), 2.17 - 2.05 (m, 4H), 2.01 - 1.92 (m, 1H)。

Example 8



Step 1

Compound **1-13B** (100 mg, 127 μmol), compound **8-1** (63.4 mg, 280 μmol), triethylamine (509 μmol, 70.9 μL) were dissolved in DMF (1.00 mL), nitrogen was replaced three times, and the reaction was performed at 50°C for six hours. 10.0 mL of water was added to the reaction solution, and extracted three times with ethyl acetate (20.0 mL). The organic phase was washed with saturated brine (50.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude product was purified to compound **8-2** by preparation of a thin layer of chromatography (petroleum ether: ethyl acetate = 3:1). MS m/z = 862.4$[M+H]^+$.

Step 2

Compound **8-2** (60.0 mg, 69.6 μmol) was dissolved in anhydrous methylene chloride (1.00 mL), metachloroperoxybenzoic acid (15.5 mg, 76.6 μmol 85.0% purity) was added in batches at 0°C, and then reacted at room temperature for 1 hour. 10.0 mL of sodium bicarbonate solution and 10.0 mL of sodium sulfate solution were added to the reaction solution, and extracted with dichloromethane (30.0 mL) for three times. The organic phase was washed with saturated brine (50.0 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude product was purified by preparation of thin layer of chromatography (petroleum ether: ethyl acetate = 2:1) to obtain compound **8-3**. MS m/z = 878.3$[M+H]^+$.

Step 3

Compound **8-3** (35.0 mg, 39.9 μmol) was dissolved in anhydrous toluene (1.00 mL), compound **1-2** (12.2 mg, 79.7 μmol), tert-butanol sodium (15.3 mg, 159 μmol) and 4Å molecular sieve (18.0 mg), and the reaction was carried out at 100°C for 6 hours after nitrogen replacement. The reaction solution

was concentrated under reduced pressure to obtain the crude product. The crude product was purified by preparation of a thin layer of chromatography (pure ethyl acetate) to obtain compound **8-4**. MS m/z = 967.4[M+H]$^+$.

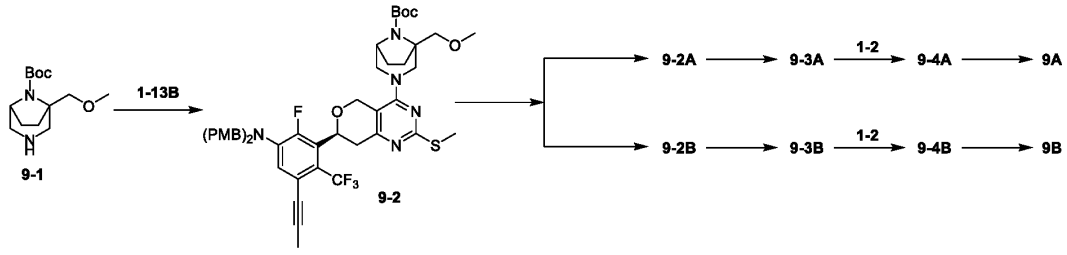
Step 4

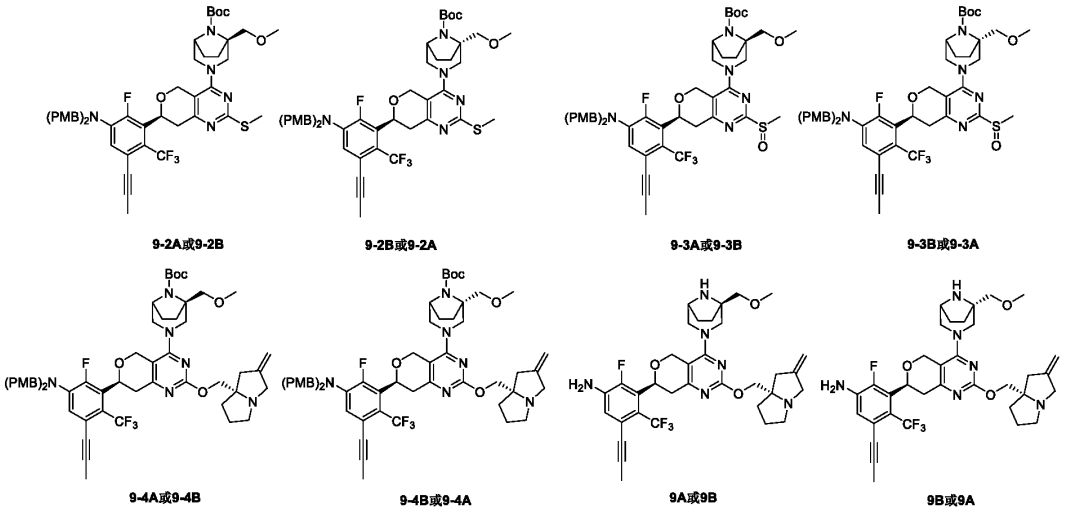
Compounds **8-4** (30.0 mg, 31.0 μmol) were dissolved in anhydrous methylene chloride (0.5 mL), trifluoroacetic acid (1.35 mmol, 100 μL) was added, and then reacted at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure to obtain the crude product, and the crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid-acetonitrile]; acetonitrile: 16%-46%. After lyophilization, the trifluoroacetate of compound **8A** and the trifluoroacetate of **8B** were obtained.

Trifluoroacetate of Compound **8A**: MS m/z = 627.3[M+H]$^+$, ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 5.31 (br d, *J* = 8.5 Hz, 2H), 5.19 (br dd, *J* = 3.6, 11.8 Hz, 1H), 4.97 - 4.93 (m, 1H), 4.73 (br d, *J* = 14.6 Hz, 1H), 4.65 - 4.45 (m, 2H), 4.34 (br d, *J* = 14.4 Hz, 1H), 4.14 (br d, *J* = 5.5 Hz, 1H), 4.03 - 3.89 (m, 3H), 3.81 - 3.70 (m, 1H), 3.42 - 3.34 (m, 1H), 3.29 - 3.23 (m, 1H), 3.22 - 3.15 (m, 1H), 3.07 - 2.91 (m, 3H), 2.81 (br d, *J* = 16.0 Hz, 1H), 2.36 (br dd, *J* = 5.9, 11.4 Hz, 2H), 2.31 - 2.10 (m, 5H), 2.06 - 1.93 (m, 4H), 1.15 (d, *J* = 6.0 Hz, 3H)。

Trifluoroacetate of Compound **8B**, MS m/z = 627.3[M+H]$^+$, ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.93 (d, *J* = 8.5 Hz, 1H), 5.31 (br d, *J* = 8.0 Hz, 2H), 5.10 - 4.99 (m, 2H), 4.75 (s, 1H), 4.57 (s, 2H), 4.33 (br d, *J* = 14.3 Hz, 1H), 4.21 - 4.09 (m, 1H), 3.98 - 3.84 (m, 3H), 3.82 - 3.71 (m, 1H), 3.45 (br dd, *J* = 11.2, 17.7 Hz, 1H), 3.28 - 3.18 (m, 2H), 3.15 - 3.01 (m, 2H), 2.92 - 2.77 (m, 2H), 2.40 - 2.11 (m, 7H), 2.03 - 1.92 (m, 4H), 1.02 (d, *J* = 6.3 Hz, 3H)。

Example 9





Step 1

Compound **1-13B** (49.0 mg, 62.4 μmol) and compound **9-1** (48.0 mg, 187 μmol) were dissolved in dichloromethane (1.00 mL), to which it was added with *N*,*N*-diisopropylethylamine (54.3 μL), and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain compound **9-2**. MS m/z = 892.4 $[M+1]^+$. The SFC was further prepared for separation (chiral column: (column: (s,s) WHELK-O1 (250mm*30mm, 10um); mobile phase: [supercritical carbon dioxide-acetonitrile/isopropanol (0.1% ammonia water)]; acetonitrile/isopropanol (0.1% ammonia water): 50%-50%. Compound **9-2A** and compound **9-2B** were obtained after concentration under reduced pressure. Analysis SFC: (chiral column: (s,s) WHELK-O1 (50 mm*4.6 mm, 3.5 μm); mobile phase: [supercritical carbon dioxide-isopropanol (0.05% diethylamine)]; isopropanol (0.05% diethylamine)%: 40%, compound **9-2A**, Rt=1.768 min, ee value 99%; MS m/z = 892.4 $[M+H]^+$; compound **9-2B**, Rt=2.286 min, 99% ee, MS m/z = 892.4 $[M+H]^+$.

Step 2

Compound **9-2A** (30.0 mg, 33.6 μmol) was dissolved in dichloromethane (1.00 mL), to which metachloroperoxybenzoic acid (8.19 mg, 40.4 μmol, 85.0% purity) was added, and the solution was reacted at 25 °C for 2 hours. The reaction solution was quenched with a saturated sodium sulfite solution, the organic phase was collected and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain compound **9-3A**. m/z = 908.4 $[M+1]^+$.

With reference to step 2, compound **9-2A** was replaced with compound **9-2B** as the raw material to obtain compound**9-3B**. m/z = 908.4 $[M+1]^+$.

Step 3

Compound **9-3A** (12.0 mg, 13.2 μmol), compound **1-2** (6.07 mg, 39.7 μmol), sodium tert-butanol (3.81 mg, 39.7 μmol) and 4Å molecular sieve (12.0 mg) were added to toluene (1.00 mL), and the reaction solution was reacted at 110 °C for 12 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by column chromatography (dichloromethane: methanol = 10:1) to obtain compound **9-4A**. MS m/z = 997.6 $[M+1]^+$.

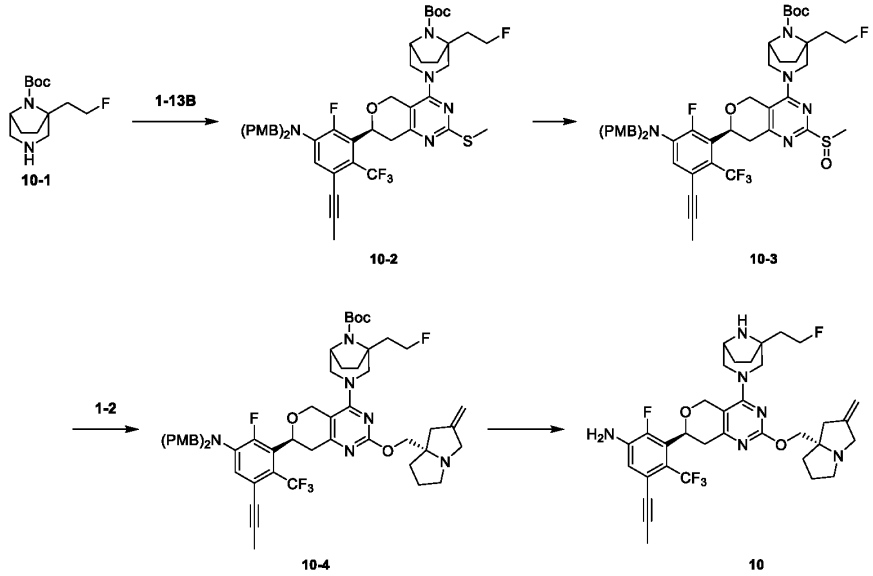
With reference to step 3, compound **9-3A** was replaced with compound **9-3B** as the raw material to obtain compound**9-4B**. MS m/z = 997.6 $[M+1]^+$.

Step 4

Compound **9-4A** (10.0 mg, 10.0 μmol) was dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 15%-45% purification to obtain **9A** of trifluoroacetate. MS m/z = 657.4 $[M+1]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.97 - 6.92 (m, 1H), 5.33 (br d, *J* = 7.8 Hz, 2H), 5.28 - 5.17 (m, 1H), 4.76 - 4.72 (m, 1H), 4.56 (s, 2H), 4.41 - 4.28 (m, 2H), 4.22 - 4.15 (m, 1H), 3.99 - 3.91 (m, 1H), 3.79 - 3.63 (m, 5H), 3.52 - 3.48 (m, 3H), 3.35 (br d, *J* = 1.8 Hz, 1H), 3.31 - 3.23 (m, 3H), 3.09 - 2.79 (m, 3H), 2.40 - 2.10 (m, 6H), 2.04 (s, 3H), 2.01 - 1.88 (m, 2H)。

Compounds **9-4B** (13.0 mg, 13.0 μmol) were dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Preparation of crude product High performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 15%-45% purification to obtain **9B** of trifluoroacetate. MS m/z = 657.5 $[M+1]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, *J* = 8.5 Hz, 1H), 5.33 (br d, *J* = 7.6 Hz, 2H), 5.26 - 5.18 (m, 1H), 4.78 - 4.73 (m, 1H), 4.57 (s, 2H), 4.39 - 4.28 (m, 2H), 4.17 - 4.12 (m, 1H), 3.94 (br d, *J* = 14.4 Hz, 1H), 3.85 - 3.63 (m, 5H), 3.50 (s, 3H), 3.41 - 3.34 (m, 2H), 3.31 - 3.21 (m, 2H), 3.09 - 2.78 (m, 3H), 2.41 - 2.12 (m, 6H), 2.04 (s, 3H), 2.02 - 1.91 (m, 2H)。

Example 10



Step 1

Compound **1-13B** (49.0 mg, 62.4 μmol) and compound **10-1** (48.0 mg, 187 μmol) were dissolved in dichloromethane (1.00 mL), to which *N,N*-diisopropylethylamine (40.3 mg, 312 μmol, 54.3 μL) was added, and the solution was reacted under 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to obtain compound **10-2**. MS m/z = 894.4 $[M+1]^+$.

Step 2

Compound **10-2** (50.0 mg, 55.9 μmol) was dissolved in dichloromethane (1.00 mL), to which m-chloroperoxybenzoic acid (13.6 mg, 67.1 μmol, 85.0% purity) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was quenched with a saturated sodium sulfite solution, the aqueous phase was extracted with dichloromethane (10.0 mL*2), the organic phase was collected and concentrated to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain compound **10-3**. m/z = 910.3 $[M+1]^+$.

Step 3

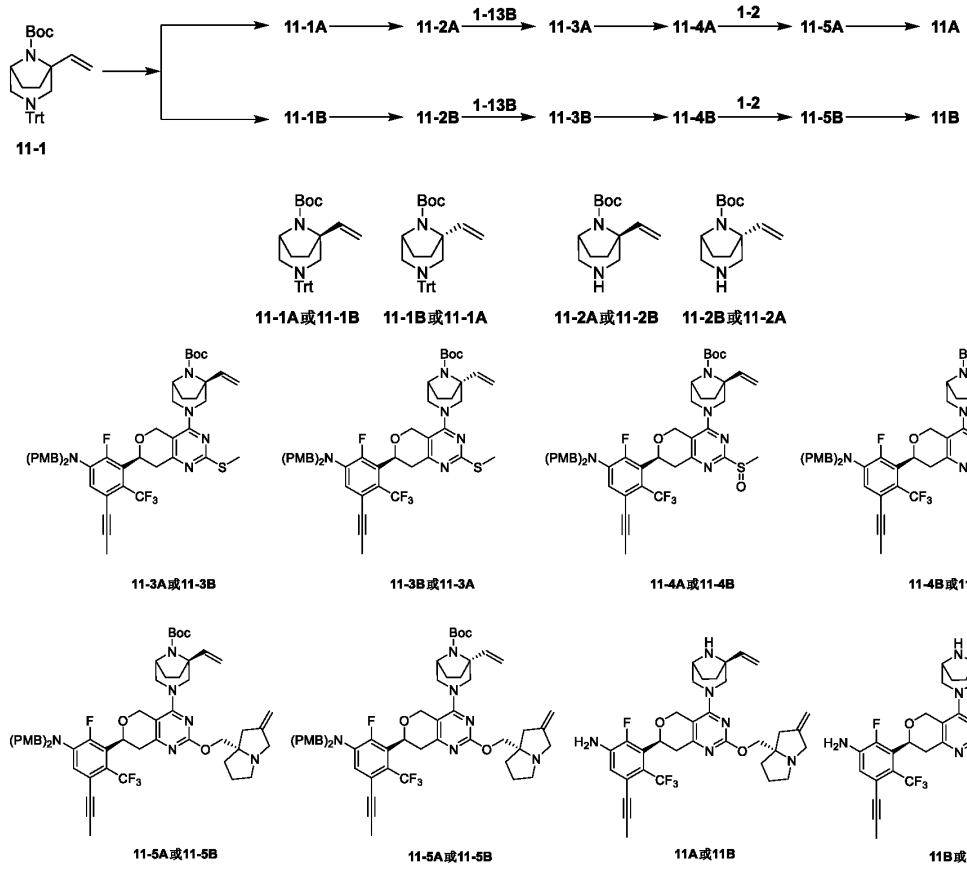
Compound **10-3** (30.0 mg, 32.9 μmol), compound **1-2** (15.2 mg, 98.9 μmol), sodium tert-butanol (9.50 mg, 98.9 μmol) and 4Å molecular sieve (30.0 mg) were added to toluene (1.00 mL), and the reaction solution was reacted at 110 °C for 12 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by column chromatography (dichloromethane: methanol = 10:1) to obtain compound **10-4**. MS m/z = 999.6 $[M+1]^+$.

Step 4

Compound **10-4** (25.0 mg, 25.0 μmol) was dissolved in dichloromethane (1.00 mL), to which

trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product High performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 12%-42% purification to obtain **10** trifluoroacetate salt. MS m/z = 659.3 $[M+1]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 5.54 - 5.52 (m, 1H), 5.31 (br d, *J* = 7.6 Hz, 2H), 5.23 - 5.13 (m, 1H), 4.94 - 4.90 (m, 1H), 4.85 - 4.63 (m, 5H), 4.62 - 4.25 (m, 4H), 4.23 - 4.11 (m, 1H), 3.97 - 3.67 (m, 4H), 3.40 - 3.33 (m, 1H), 3.28 - 3.22 (m, 1H), 3.10 - 2.89 (m, 2H), 2.80 (br d, *J* = 15.9 Hz, 1H), 2.44 - 2.33 (m, 2H), 2.27 - 2.11 (m, 5H), 2.02 (s, 3H), 1.98 - 1.91 (m, 1H)。

Example 11



Step 1

Compound **11-1** was prepared for SFC separation (chiral column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 um; mobile phase: [supercritical carbon dioxide-acetonitrile/isopropanol (0.1% ammonia water)]; acetonitrile/isopropanol (0.1% ammonia water): 30%-30%. Compound **11-1A** and compound **11-1B** were obtained after concentration under reduced pressure. Analysis SFC: (chiral

column: DAICEL CHIRALPAK AD (50 mm*4.6 mm, 3 μm); mobile phase: [supercritical carbon dioxide-isopropanol (0.05% diethylamine]; isopropanol (0.05% diethylamine)%: 5%-40%, compound **11-1A**, Rt=1.308 min, ee value 99%; MS m/z = 503.2 $[M+Na]^+$; compound **11-1B**, Rt=1.499 min, 99% ee, MS m/z = 503.2 $[M+Na]^+$.

Step 2

Compound **11-1A** (238 mg, 495 μmol) was dissolved in acetic acid (4.00 mL), and the acetic acid was concentrated under reduced pressure at 25 °C for 12 hours to remove the acetate salt of compound **11-2A**.

With reference to Step 2, Compound **11-1B** was used as the raw material to replace Compound **11-1A** to obtain the acetate salt of Compound **11-2B**.

Step 3

Compounds **1-13B** (200 mg, 254 μmol), compound **11-2A** (182 mg, acetate) were dissolved in dichloromethane (3.00 mL), to which was added *N,N*-diisopropylethylamine (1.27 mmol, 222 μL), and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to obtain compound **11-3A**. MS m/z = 874.4 $[M+1]^+$.

With reference to step 3, the acetate salt of compound **11-2B** was used as the raw material to replace the acetate salt of compound **11-2A** to obtain compound **11-3B**. MS m/z = 874.4 $[M+1]^+$.

Step 4

Compound **11-3A** (180 mg, 206 μmol) was dissolved in dichloromethane (3.00 mL), to which metachloroperoxybenzoic acid (43.9 mg, 216 μmol, 85.0% purity) was added, and the reaction solution was reacted at 25 °C for 2 hours. Add 10.0 mL of sodium bicarbonate solution and 10.0 mL of sodium sulfite solution to the reaction solution, extract the aqueous phase with dichloromethane (30.0 mL*2), collect the organic phase and concentrate to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain compound **11-4A**.

With reference to step 4, compound **11-3A** was replaced with compound **11-3B** as the raw material to obtain compound **11-4B**.

Step 5

Compound **11-4A** (140 mg, 157 μmol), compound **1-2** (48.2 mg, 315 μmol), sodium tert-butoxide (60.5 mg, 629 μmol) and 4Å molecular sieve (70.0 mg) were added to toluene (3.00 mL), and the solution was reacted at 110 °C for 12 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 1:2) to obtain compound **11-5A**. MS

m/z = 979.5 $[M+1]^+$.

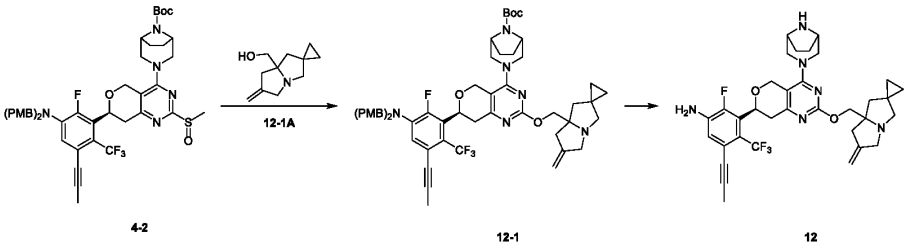
With reference to step 4, compound **11-4A** was replaced with compound **11-4B** as the raw material to obtain compound **11-5B**. MS m/z = 979.5 $[M+1]^+$.

Step 6

Compound **11-5A** (72.0 mg, 73.5 μmol) was dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.20 mL) was added, and the reaction solution was reacted at 25 °C for 2 hours. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 16%-46% purification to obtain **11A** of trifluoroacetate. MS m/z = 639.3 $[M+H]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.6 Hz, 1H), 6.15 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.61 - 5.46 (m, 2H), 5.31 (br d, *J* = 7.5 Hz, 2H), 5.25 - 5.17 (m, 1H), 5.09 - 4.97 (m, 1H), 4.77 - 4.72 (m, 2H), 4.55 (s, 2H), 4.39 - 4.22 (m, 3H), 3.98 - 3.70 (m, 3H), 3.55 (d, *J* = 13.6 Hz, 1H), 3.28 - 3.21 (m, 2H), 3.09 - 2.90 (m, 2H), 2.79 (br d, *J* = 16.3 Hz, 1H), 2.40 - 2.05 (m, 8H), 2.02 (s, 3H)。

Compounds **11-5B** (64.0 mg, 65.4 μmol) were dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.20 mL) was added, and the reaction solution was reacted at 25 °C for 2 hours. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 16%-46% purification to obtain **11B** of trifluoroacetate. MS m/z = 639.3 $[M+H]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 6.18 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.66 - 5.48 (m, 2H), 5.31 (br d, *J* = 7.4 Hz, 2H), 5.20 (br dd, *J* = 4.1, 10.9 Hz, 1H), 4.95 - 4.91 (m, 1H), 4.78 - 4.71 (m, 2H), 4.55 (s, 2H), 4.45 - 4.16 (m, 3H), 3.98 - 3.62 (m, 4H), 3.27 - 3.22 (m, 2H), 3.09 - 2.88 (m, 2H), 2.79 (br d, *J* = 16.3 Hz, 1H), 2.56 - 2.03 (m, 8H), 2.02 (s, 3H)。

Example 12



Step 1

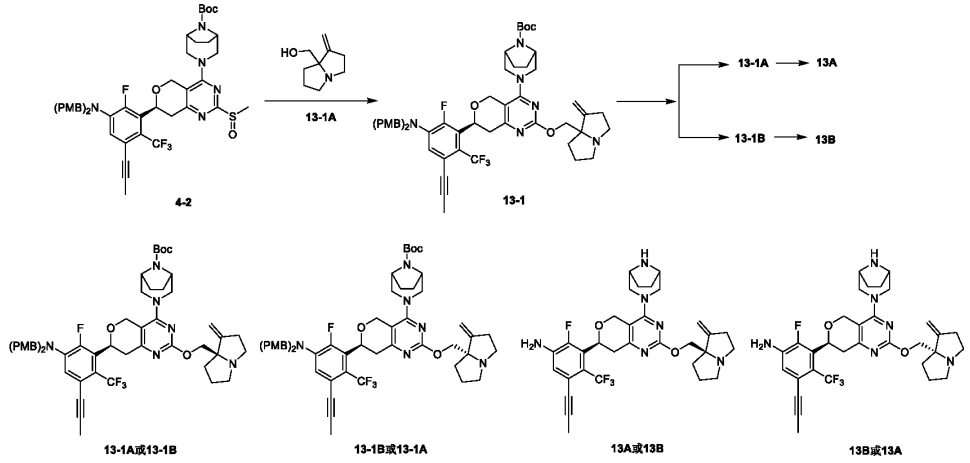
Compound **4-2** (100 mg, 115 μmol), compound **12-1A** (83.0 mg, 463 μmol), sodium tert-butoxide

(44.5 mg, 463 μmol) and 4Å molecular sieve (100.0 mg) were added to toluene (5.00 mL), and the reaction solution was reacted at 110 °C for 12 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by column chromatography (dichloromethane: methanol = 10:1) to obtain compound **12-1**. MS m/z = 979.5 $[M+1]^+$.

Step 2

Compound **12-1** (90.0 mg, 91.9 μmol) was dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 2 hours. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 16%-46% purification to obtain **12** of trifluoroacetate. MS m/z = 639.4 $[M+H]^+$, ^1H NMR (400 MHz, D_2O) δ ppm 7.12 (d, *J* = 8.5 Hz, 1H), 5.33 - 5.26 (m, 2H), 5.05 - 4.94 (m, 2H), 4.36 - 4.19 (m, 4H), 3.99 - 3.87 (m, 3H), 3.62 - 3.25 (m, 5H), 3.21 - 2.85 (m, 4H), 2.31 - 2.07 (m, 6H), 2.06 - 2.01 (m, 3H), 1.96 - 1.86 (m, 1H), 0.87 - 0.72 (m, 4H).

Example 13



Step 1

Compound **4-2** (50.0 mg, 57.9 μmol), compound **13-1A** (26.6 mg, 174 μmol), sodium tert-butanol (27.8 mg, 289 μmol) and 4 Å molecular sieve (50.0 mg) were added to toluene (2.00 mL), and the reaction solution was reacted at 110 °C for 12 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by column chromatography (dichloromethane: methanol = 10:1) to obtain compound **13-1**. MS m/z = 953.5 $[M+1]^+$. Compound **13-1** was prepared for SFC separation (chiral column: (s,s)

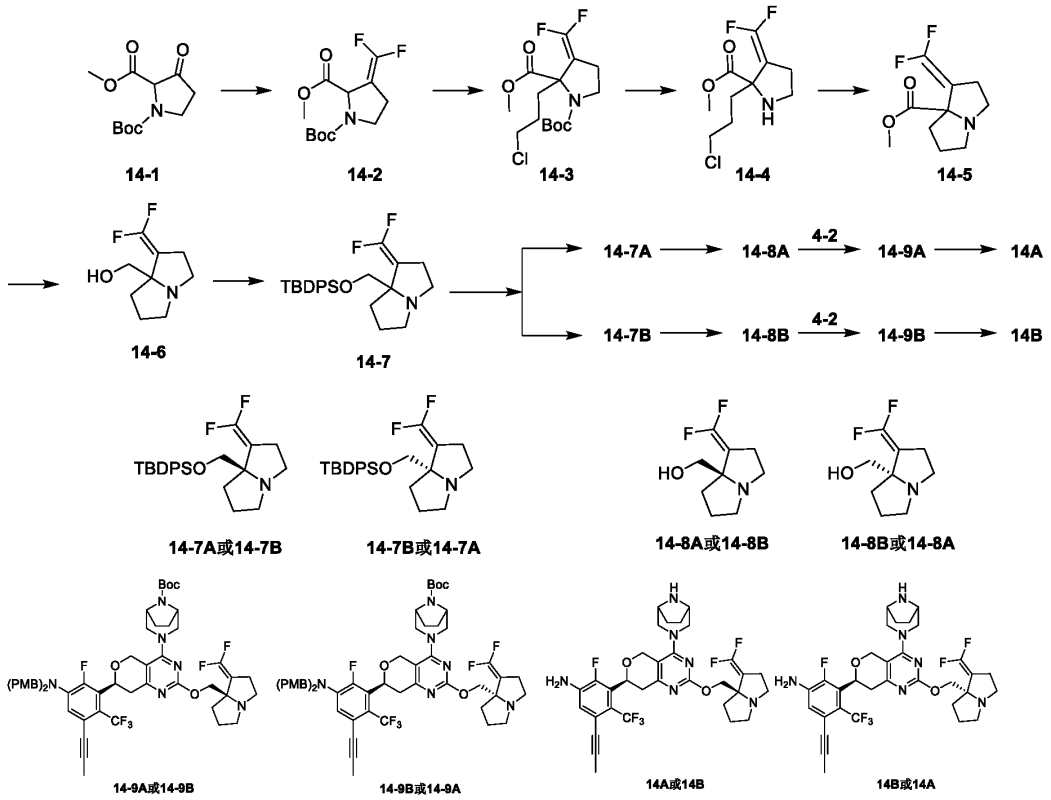
WHELK-O1 (250 mm * 30 mm, 10 um); mobile phase: [supercritical carbon dioxide-acetonitrile/isopropanol (0.1% ammonia water)]; acetonitrile/isopropanol (0.1% ammonia water): 38%-38%, and compound **13-1A** and compound **13-1B** were obtained after concentration under reduced pressure. Analyze SFC: (Chiral column: (s,s) WHELK-O1 (50 mm*4.6 mm, 3.5 μm); mobile phase: [supercritical carbon dioxide-isopropanol (0.05% diethylamine)]; isopropanol (0.05% diethylamine)%: 40%, compound **13-1A**, Rt=1.495 min, ee value 99%; MS m/z = 953.5 $[M+H]^+$; compound **13-1B**, Rt=1.716 min, ee value 95%, MS m/z = 953.5 $[M+H]^+$.

Step 2

Compound **13-1A** (17.0 mg, 17.8 μmol) was dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated directly to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 10%-40% purification to obtain **13A** of trifluoroacetate. MS m/z =613.4 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 5.41 - 5.27 (m, 2H), 5.18 (br dd, *J* = 3.8, 10.8 Hz, 1H), 4.77 - 4.70 (m, 1H), 4.68 - 4.50 (m, 2H), 4.32 (br d, *J* = 14.4 Hz, 1H), 4.22 - 4.10 (m, 2H), 3.88 - 3.63 (m, 4H), 3.48 - 3.32 (m, 4H), 3.27 (br d, *J* = 12.1 Hz, 1H), 3.03 - 2.88 (m, 3H), 2.53 - 2.40 (m, 1H), 2.32 - 2.09 (m, 6H), 2.04 - 2.01 (m, 3H), 2.01 - 1.93 (m, 1H)。

Compound **13-1B** (20.0 mg, 21.0 μmol) was dissolved in dichloromethane (1.00 mL), to which trifluoroacetic acid (0.30 mL) was added, and the reaction solution was reacted at 25 °C for 1 hour. The reaction solution was concentrated directly to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 10%-40% purification to obtain **13B** of trifluoroacetate. MS m/z =613.5 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, *J* = 8.5 Hz, 1H), 5.44 - 5.30 (m, 2H), 5.20 (dd, *J* = 3.8, 11.3 Hz, 1H), 4.79 - 4.73 (m, 1H), 4.70 - 4.56 (m, 2H), 4.39 (br d, *J* = 14.0 Hz, 1H), 4.22 - 4.13 (m, 2H), 3.88 - 3.69 (m, 4H), 3.47 - 3.34 (m, 4H), 3.32 - 3.27 (m, 1H), 3.01 - 2.94 (m, 3H), 2.53 - 2.40 (m, 1H), 2.32 - 2.12 (m, 6H), 2.04 (s, 3H), 2.02 - 1.94 (m, 1H)。

Example 14



Step 1

Compound **14-1** (5.00 g, 20.6 mmol) was dissolved in DMF (50.0 mL), then triphenylphosphoniumyl difluoroacetate (19.0 g, 53.4 mmol) was added and reacted at 80 °C for 2 hours. Add water (300 mL) to the reaction solution, and extract with ethyl acetate (10 mL) three times. The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 100:1-3:1) to obtain compound **14-2**. ^{1}H NMR (400 MHz, $CDCl_3$) 5.00 - 4.76 (m, 1H), 3.82 - 3.65 (m, 4H), 3.61 - 3.45 (m, 1H), 2.71 - 2.55 (m, 2H), 1.49 - 1.38 (m, 9H).

Step 2

Compound **14-2** (2.80.g, 10.1 mmol) was dissolved in tetrahydrofuran (3.00 mL), lithium diisopropylamide (2.00 M, 10.1 mL) was added, 1-chloro-3-iodopropane (10.3 g, 50.5 mmol, 1.55 mL) was added after reaction at -60 °C for 1 hour, then 1 hours at -60 °C, and 12 hours at 25 °C. To the reaction solution was added 50.0 mL of ammonium chloride solution and extracted 3 times with ethyl acetate (50.0 mL). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 50:1-10:1) to obtain

compound **14-3**. MS m/z = 376.1[M+Na]$^+$.

Step 3

Compound **14-3** (3.20 g, 9.04 mmol) was dissolved in acetonitrile (1.00 mL), hydrochloric acid/dioxane (2.00 M, 5.00 mL) was added and reacted at 25 °C for 12 hours. The solvent was removed by concentration under reduced pressure to obtain the hydrochloride salt of compound **14-4**. MS m/z = 254.1[M+H]$^+$.

Step 4

Compound **14-4** (2.50 g, hydrochloride) was dissolved in acetonitrile (25.0 mL), potassium carbonate (5.95 g, 43.1 mmol) and potassium iodide (143 mg, 862 μmol) were added, and the reaction was performed at 25 °C for 12 hours, filtered, concentrated to obtain the crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 50:1-20:1) to obtain compound **14-5**. MS m/z = 218[M+H]$^+$.

Step 5

Compound **14-5** (300 mg, 1.38 mmol) was dissolved in THF (3.00 mL), lithium aluminum hydride (2.50 M, 1.10 mL) was added, and then reacted at 0 ° C for 1 hour. 0.11 mL of water, 0.11 mL of 15% sodium hydroxide solution, and 0.33 mL of water were added into the reaction solution, filtered, concentrated to obtain compound **14-6**. MS m/z = 190.1[M+H]$^+$.

Step 6

Compounds **14-6** (300 mg, 1.59 mmol) were dissolved in anhydrous methylene chloride (3.00 mL), imidazole (432 mg, 6.34 mmol), 4-dimethylaminopyridine (19.37 mg, 159 μmol) and tert-butylchlorodiphenylsilane (872 mg, 3.17 mmol, 812 μL) were added and reacted at 25 °C for 12 hours. The reaction solution was concentrated to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 25%-55%) to obtain compound **14-7**. MS m/z = 428.3[M+H]$^+$. Compound **14-7** was prepared for SFC separation (chiral column: DAICEL CHIRALCEL OX (250 mm*50 mm, 10 um); mobile phase: [supercritical carbon dioxide-methanol (0.1% ammonia)]; methanol (0.1% ammonia) is 10%-10%. After concentration under reduced pressure, compound **14-7A** and compound **14-7B** were obtained. Analyze SFC: (Chiral column: DAICEL CHIRALCEL OX (50mm*4.6mm, 3μm); mobile phase: [supercritical carbon dioxide-methanol (0.05% diethylamine)]; methanol (0.05% diethylamine)]; methanol (0.05% diethylamine): 5%-40%, compound **14-7A**, Rt=1.165 min, ee value 99%; MS m/z = 428.2 [M+H]$^+$; compound **14-7B**, Rt=1.233 min, ee value 95% MS m/z = 428.2 [M+H]$^+$.

Step 7

Compounds **14-7A** (126 mg, 295 μmol) were dissolved in dioxane (2.00 mL), hydrochloric acid (12

M, 0.50 mL) was added, and reacted at 95 °C for 12 hours. Add 2 mL of water to dissolve, extract with ethyl acetate (10 mL), and obtain the hydrochloride salt of compound **14-8A** from the lyophilized aqueous phase. MS m/z = 190.1[M+H]$^+$.

With reference to step 7, compound **14-7A** was replaced with compound **14-7B** as the raw material to obtain the hydrochloride salt of compound **14-8B**. MS m/z = 190.1[M+H]$^+$.

Step 8

Compound **4-2** (120 mg, 139 μmol), compound **14-8A** (62.7 mg, hydrochloride), sodium tert-butanol (66.7 mg, 695 μmol) and 4Å molecular sieve (30.0 mg) were added to toluene (3.00 mL), and the reaction solution was reacted at 100 °C for 6 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by thin layer chromatography (pure ethyl acetate) to obtain compound **14-9A**. MS m/z = 989.7 [M+1]$^+$.

With reference to step 8, compound **14-8A** was replaced with compound **14-8B** as the raw material to obtain compound**14-9B**. MS m/z = 989.6 [M+H]$^+$.

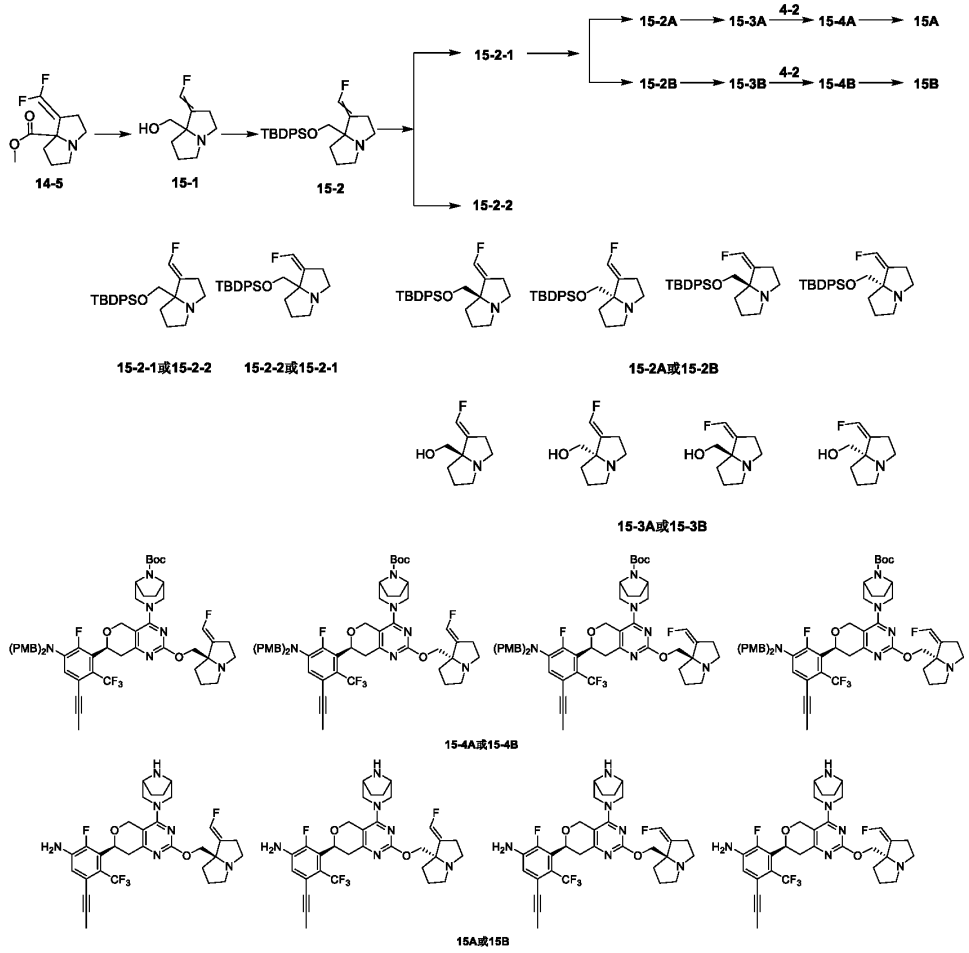
Step 9

Compound **14-9A** (63.0 mg, 63.7 μmol) was dissolved in dichloromethane (4.00 mL), to which trifluoroacetic acid (1.00 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 16%-46% purification to obtain **14A** of trifluoroacetate. MS m/z =649.2 [M+H]$^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 5.19 (br dd, *J* = 3.9, 11.1 Hz, 1H), 4.96 - 4.90 (m, 1H), 4.84 - 4.78 (m, 1H), 4.77 - 4.70 (m, 2H), 4.66 - 4.58 (m, 1H), 4.32 (br d, *J* = 14.0 Hz, 1H), 4.15 (br dd, *J* = 3.0, 13.6 Hz, 2H), 3.97 - 3.63 (m, 4H), 3.57 - 3.39 (m, 2H), 3.36 - 3.33 (m, 1H), 3.09 - 2.87 (m, 3H), 2.49 - 2.05 (m, 7H), 2.04 - 1.93 (m, 4H)。

Compound **14-9B** (88.0 mg, 89.0 μmol) was dissolved in dichloromethane (4.00 mL), to which trifluoroacetic acid (1.00 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 16%-46% purification to obtain **14B** of trifluoroacetate. MS m/z =649.2 [M+H]$^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 6.92 (d, *J* = 8.5 Hz, 1H), 5.19 (br dd, *J* = 4.1, 11.3 Hz, 1H), 4.93 - 4.88 (m, 2H), 4.80 - 4.70 (m, 2H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.30 (br d, *J* = 14.1 Hz, 1H), 4.15 (br dd, *J* = 2.1, 14.3

Hz, 2H), 3.95 - 3.62 (m, 4H), 3.58 - 3.38 (m, 2H), 3.30 - 3.24 (m, 1H), 3.09 - 2.87 (m, 3H), 2.47 - 2.07 (m, 7H), 2.05 - 1.94 (m, 4H)。

Example 15



Step 1

Compounds **14-5** (500 mg, 2.30 mmol) were dissolved in 2-MeTHF (5.00 mL), bis(2-methoxyethoxy)aluminum sodium hydride (2.66 g, 9.21 mmol, 2.57 mL, 70% purity) was added and reacted at 10 ° C for 2.5 hours. Then it was reacted at room temperature for 12 hours, 10.0 mL of water was added to the reaction solution, concentrated to remove dimethyltetrahydrofuran, and lyophilized to obtain compound **15-**1. MS m/z = 172.1$[M+H]^+$.

Step 2

Compound **15-1** (261 mg, 1.52 mmol) was dissolved in anhydrous methylene chloride (3.00 mL), imidazole (415 mg, 6.10 mmol), 4-dimethylaminopyridine (18.6 mg, 152 μmol) and tert-butylchlorodiphenylsilane (838 mg, 3.05 mmol, 780 μL) were added and reacted at 45 °C for 12 hours.

The reaction solution was concentrated to obtain the crude product. Crude product was performed with the preparation of high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 35%-65% to obtain compound **15-2**, MS m/z = 410.3[M+H]$^+$. Compound **15-2** was prepared for SFC separation (chiral column: DAICEL CHIRALPAK IG(250mm*50mm, 10um); mobile phase: [supercritical dichloromethane-methanol (0.1% ammonia water]); methanol (0.1% ammonia water): 18%-18%); after concentration under reduced pressure, compound **15-2-1** and compound **15-2-2** were obtained. Analyze SFC: (Chiral column: Chiralcel OX-3 (50mm*4.6mm, 3μm); mobile phase: [supercritical carbon dioxide-ethanol (0.05% diethylamine]); ethanol (0.05% diethylamine)%: 5%-40%, compound **15-2-1**, Rt=1.18 min, ee value 99%; MS m/z = 410.2[M+H]$^+$; compound **15-2-2**, Rt=1.46 min, ee value 97% MS m/z = [410.2M+H]+.

Chiral preparation HPLC separation of compound **15-2-1** was performed (chiral column: DAICEL CHIRALCEL OX (250 mm * 50 mm, 10 μm); mobile phase: [n-hexane-ethanol (0.1% ammonia water)]; ethanol (0.1% ammonia water, 10%-10%. After concentration under reduced pressure, compound **15-2A** and compound **15-2B** were obtained. Analyze SFC: (Chiral column: Chiralcel OX-3 (50mm*4.6mm, 3μm); mobile phase: [supercritical carbon dioxide-ethanol (0.05% diethylamine]); ethanol (0.05% diethylamine) %: 5%-40%, compound **15-2A**, Rt=1.18 min, ee value 99%; MS m/z = 410.2[M+H]$^+$; compound **15-2B**, Rt=1.21 min, ee value 99% MS m/z = 410.2 [M+H]$^+$.

Step 3

Compound **15-2A** (160 mg, 391 μmol) was dissolved in dioxane (4.00 mL), hydrochloric acid (12 M, 1.00 mL) was added and reacted at 95 °C for 12 hours. Add 5 mL of water to dissolve, extract with ethyl acetate (3.0 mL), and obtain the hydrochloride salt of compound **15-3A** from the lyophilized aqueous phase. MS m/z = 172.1[M+H]$^+$.

With reference to step 3, compound **15-2B** was replaced with compound **15-2A** as the raw material to obtain the hydrochloride salt of compound **15-3B**. MS m/z = 172.1[M+H] $^+$.

Step 4

Compound **4-2** (100 mg, 116 μmol), compound **15-3A** (48.1 mg, hydrochloride), sodium tert-butanol (55.6 mg, 579 μmol) and 4Å molecular sieve (50.0 mg) were added to toluene (3.00 mL), and the reaction solution was reacted at 100 °C for 6 hours. The reaction solution was cooled to room temperature, filtered, and the filtrate was concentrated to obtain the crude product. The crude product was purified by preparing a thin layer of chromatography separation (pure ethyl acetate) to obtain compound **15-4A**. MS m/z = 971.4 [M+1]$^+$.

With reference to Step 4, the hydrochloride of compound **15-3B** was used as the raw material to replace the hydrochloride of Compound **15-3A** to obtain compound **15-4B**. MS m/z = 971.4 [M+H]

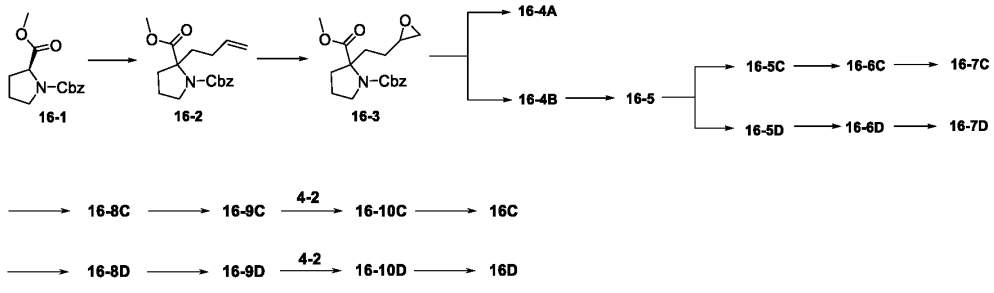
$^{+}$.

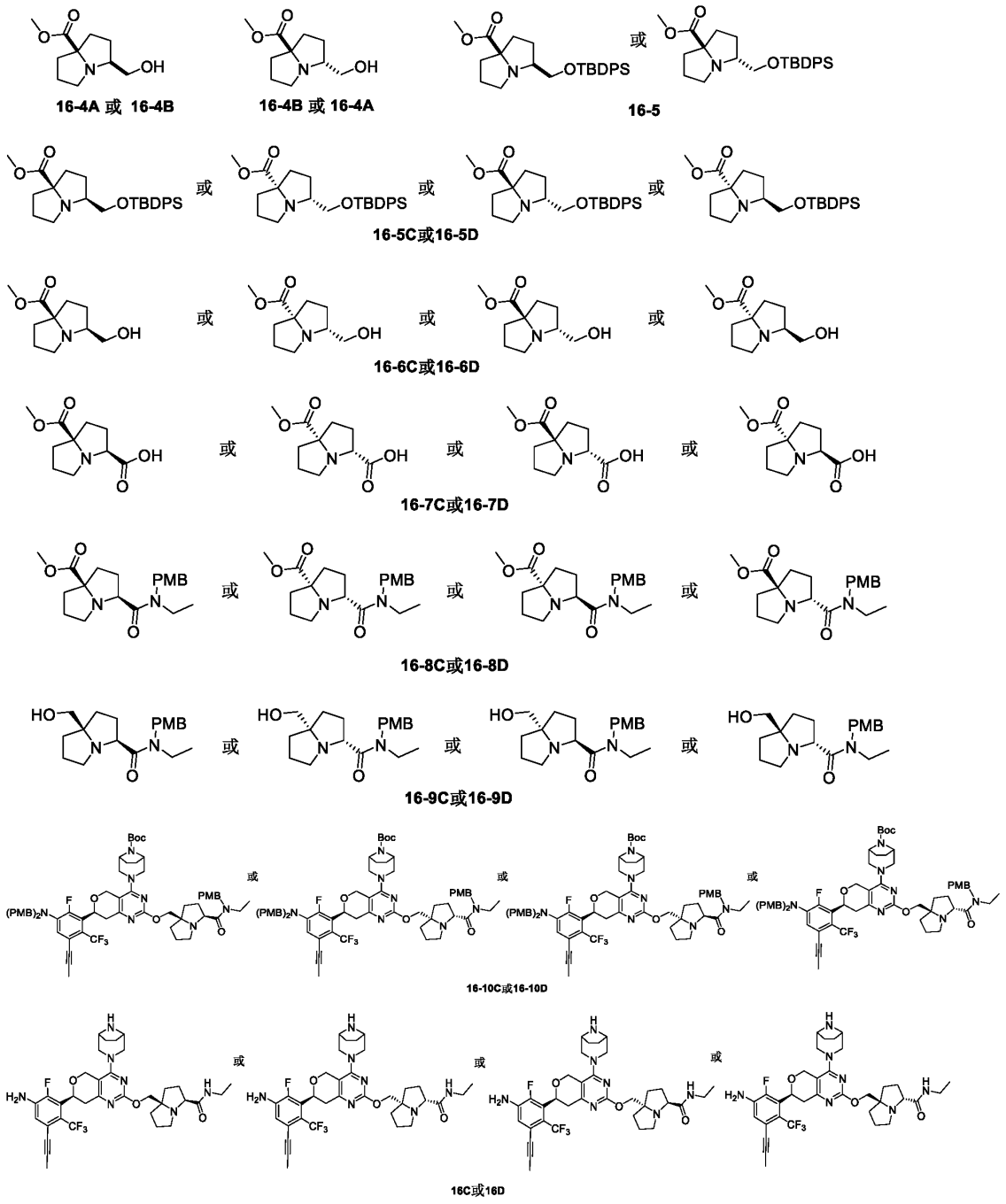
Step 5

Compound **15-4A** (71.0 mg, 73.1 μmol) was dissolved in dichloromethane (5.00 mL), to which trifluoroacetic acid (1.00 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water (0.1% ammonia)-acetonitrile]; acetonitrile: 35%-65% purification to obtain compound **15A**. MS m/z =631.3 $[M+H]^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 6.99 - 6.71 (m, 2H), 5.14 (br dd, *J* = 4.1, 11.5 Hz, 1H), 4.81 - 4.76 (m, 2H), 4.20 - 4.09 (m, 3H), 3.61 - 3.38 (m, 4H), 3.26 - 3.00 (m, 4H), 2.90 - 2.58 (m, 5H), 2.25 - 2.10 (m, 1H), 2.07 - 1.60 (m, 10H).

Compound **15-4B** (61.0 mg, 62.8 μmol) was dissolved in dichloromethane (5.00 mL), to which trifluoroacetic acid (1.00 mL) was added, and the reaction solution was reacted at 25 °C for 12 hours. The reaction solution was concentrated directly to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (column: Phenomenex luna C18 150*25mm*10μm; mobile phase: [water (0.075% trifluoroacetic acid)-acetonitrile]; acetonitrile: 10%-40% purification to obtain **15B** of trifluoroacetate. MS m/z =631.3 $[M+H]^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 7.27 - 6.84 (m, 2H), 5.19 (br dd, *J* = 3.5, 11.0 Hz, 1H), 4.79 - 4.50 (m, 4H), 4.34 (br d, *J* = 14.3 Hz, 1H), 4.15 (br dd, *J* = 2.9, 14.6 Hz, 2H), 3.91 - 3.61 (m, 4H), 3.49 - 3.33 (m, 3H), 3.30 - 3.24 (m, 1H), 3.17 - 2.87 (m, 3H), 2.54 - 2.05 (m, 7H), 2.04 - 1.92 (m, 4H).

Example 16





Step 1

The solution of tetrahydrofuran (569.72 mL, 569.72 mmol, 1M) of ditrimethylsilylaminolithium was slowly added dropwise to the solution of compound **16-**1 (100.00 g, 379.81 mmol) in tetrahydrofuran (1000 mL) at -70 °C for 1 hour. 4-bromo-1-butene (128.19 g, 949.53 mmol) was added dropwise to the reaction solution at -70 °C, and the reaction was stirred at 20 °C for 12 hours. Added 1000 mL of saturated aqueous ammonium chloride solution for quench reaction, extracted with ethyl acetate (700

mL * 3), dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, separated for column chromatography(petroleum ether: ethyl acetate = 9:1) to yielded compound **16-2**, MS m/z = 318.0 $[M+H]^+$.

Step 2

Compound **16-2** (96.00 g, 302.48 mmol) was dissolved in dichloromethane (1,000 mL), metachloroperoxybenzoic acid (135.10 g, 665.45 mmol, 85% purity) was added, and the reaction was stirred and reacted at 20 °C for 12 hours under nitrogen protection. The reaction was quenched by adding saturated sodium sulphite aqueous solution (1500 mL), washed with saturated sodium bicarbonate aqueous solution (1000 mL), the organic phase separated and dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and column chromatography separated (petroleum ether:ethyl acetate = 6:1) to obtain compound **16-3**, MS m/z = 334.1 $[M+H]^+$.

Step 3

For solution of compound **16-3** (79.00 g, 236.97 mmol) in methanol (1,500 mL), palladium/carbon (16.64 g, 156.40 mmol, 10% purity) was added and reacted at 20 °C for 16 hours in a hydrogen gas (15 psi). The filtrate was filtered and concentrated under reduced pressure, and column chromatography separation was performed (dichloromethane: methanol = 20:1 to 9:1) to obtain compound **16-4A** (drilling agent: dichloromethane: methanol = 15:1, Rf = 0.5) and compound **16-4B** (drilling agent: dichloromethane: methanol = 15:1, Rf = 0.3), respectively. Compound **16-4A**: MS m/z = 200.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.71 (s, 3H), 3.60 (dd, *J* = 12.0 Hz, 4.0 Hz,1H), 3.41 (dd, *J* = 12.0 Hz, 4.0 Hz,1H), 3.13 - 3.05 (m, 1H), 2.99 - 2.94 (m, 1H), 2.73 - 2.67 (m, 1H), 2.36 - 2.31 (m, 1H), 2.24 - 2.20 (m, 1H), 1.93 - 1.79 (m, 5H), 1.74 - 1.66 (m, 1H). **Compounds 16-4B:** MS m/z = 200.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.90 (dd, *J* = 12.0 Hz, 8.0 Hz,1H), 3.79 (dd, *J* = 12.0 Hz, 5.2 Hz,1H), 3.73 (s, 3H), 3.49 - 3.42 (m, 1H), 3.11 - 3.07 (m, 1H), 2.76 - 2.69 (m, 1H), 2.58 - 2.52 (m, 1H), 2.29 - 2.21 (m, 1H), 1.89 - 1.80 (m, 4H), 1.67 - 1.54 (m, 2H).

Step 4

Compound **16-4B** (21.00 g, 105.40 mmol) was dissolved in dichloromethane (200 mL), imidazole (15.07 g, 221.33 mmol) was added at 0 °C, tert-butylchlorodiphenylsilane (37.66 g, 137.02 mmol) was added after stirring for 10 minutes, and the temperature was increased to 20 °C for stirring for 7 hours. Filtration, concentration of filtrate under reduced pressure, column chromatography separation (petroleum ether: Ethyl acetate = 8:1) to obtain compound **16-5**, MS m/z = 438.0 $[M+H]^+$. The chiral preparation HPLC separation (chromatographic column: Regis:S,S) Whelk-O 1, 25*250 mm 10 μm; mobile phase: A: n-hexane, B: ethanol; B%: 2 % to obtain compound **16-5C** and compound **16-5D**. SFC analytical method (column: Regis (s,s) WHELK-01(4.6 mmI.D*150 mmL, 5 μm); mobile phase:

[supercritical carbon dioxide-methanol (0.05%diethylamine]; gradient: methanol (0.05%diethylamine)%: 5%-40%, 4 min), compound **16-5C**, Rt=3.640 min, ee value 97.06%, MS m/z = 438.0 $[M+H]^+$; compound **16-5D**, Rt=3.826 min, ee value 97.88%, MS m/z = 438.0 $[H]^+$.

Step 5

Compound **16-5C** (12.00 g, 27.42 mmol) was dissolved in hydrogen chloride/1, 4-dioxane solution (100 mL, 4M), and the reaction was stirred at 50 °C for 16 hours. The reaction solution was concentrated under reduced pressure, and column chromatography separated (dichloromethane: methanol = 7:1) to obtain compound **16-6C**. MS m/z =200.0 $[M+H]^+$.

With reference to step 5, compound **16-5C** was replaced with compound **16-5D** as the raw material to obtain compound **16-6D**. MS m/z = 200.0 $[M+H]^+$.

Step 6

Compound **16-6C** (1.00 g, 5.02 mmol) was dissolved in 10 mL of mixed solvent (acetonitrile: water = 100:0.75), chromium trioxide (150.56 mg 1.51 mmol) and periodic acid (2.86 g, 12.55 mmol) were added at 0 °C, and the solution was stirred under nitrogen protection for 16 hours. The reaction solution was filtered, and the filtrate was concentrated under reduced pressure to obtain compound **16-7C**. MS m/z = 214.0 $[M+H]^+$.

With reference to step 6, compound **16-6C** was replaced with compound **16-6D** as the raw material to obtain compound **16-7D**. MS m/z = 214.0 $[M+H]^+$.

Step 7

Compound **16-7C** (0.20 g, 0.94 mmol) was dissolved in N,N dimethylformamide (5 mL), followed by addition of N-ethyl-4-methoxybenzylamine (154.98 mg, 0.94 mmol), N,N-diisopropylethylamine (606.12 mg, 4.69 mmol 2-(7-azobenzotriazazole)-N,N,N',N'-tetramethylurea hexafluorophosphate phosphate (713.28, 1.88 mmol), and reaction was stirred at room temperature for 1 hour. Add water (50 mL) to the reaction solution, extract with ethyl acetate (20 mL * 3), combine the organic phases, wash with saturated brine (50 mL), dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure, and separate by column chromatography (petroleum ether: ethyl acetate = 2:1 to obtain compound **16-8C**. MS m/z =361.0 $[M+H]^+$.

With reference to step 7, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **16-8D**. MS m/z =361.0 $[M+H]^+$.

Step 8

Compounds **16-8C** (150 mg, 0.42 mmol) were dissolved in anhydrous methanol (3 mL), cooled to 0 °C, followed by sodium borohydride (50 mg, 1.25 mmol in sodium methoxide/methanol solution (7.49 mg, 41.62 μmol, 30% purity), and the reaction was stirred at room temperature for 8 hours. The reaction was quenched by adding saturated aqueous solution (10 mL) of ammonium chloride,

extracted with ethyl acetate (20 mL * 3), combined with organic phase, washed with saturated brine (20 mL), dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and separated by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain compound **16-9C**. MS m/z = 333.3 $[M+H]^+$.

With reference to step 8, compound **16-8C** was replaced with compound **16-8D** as the raw material to obtain compound **16-9D**. MS m/z =333.3 $[M+H]^+$.

Step 9

Compound **16-9C** (0.10 g, 0.30 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL), cooled to 0 °C, sodium hydrogen (60.16 mg, 1.50 mmol, 60% purity) was added, and compound **4-2** (264.70 mg, 0.30 mmol) was added after stirring at 0 °C for half an hour, and the reaction was stirred at room temperature for 1 hour. Add saturated aqueous solution of ammonium chloride (10 mL) and quench, extract with ethyl acetate (20 mL * 3), combine the extracted organic phases, wash with saturated esophagus saline (20 mL), dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure, and perform column chromatography separation (petroleum ether: ethyl acetate = 2:1) to obtain compound **16-10C**. MS m/z =1132.5 $[M+H]^+$.

With reference to step 9, compound **16-9C** was replaced with compound **16-9D** as the raw material to obtain compound **16-10D**. MS m/z =1132.5 $[M+H]^+$.

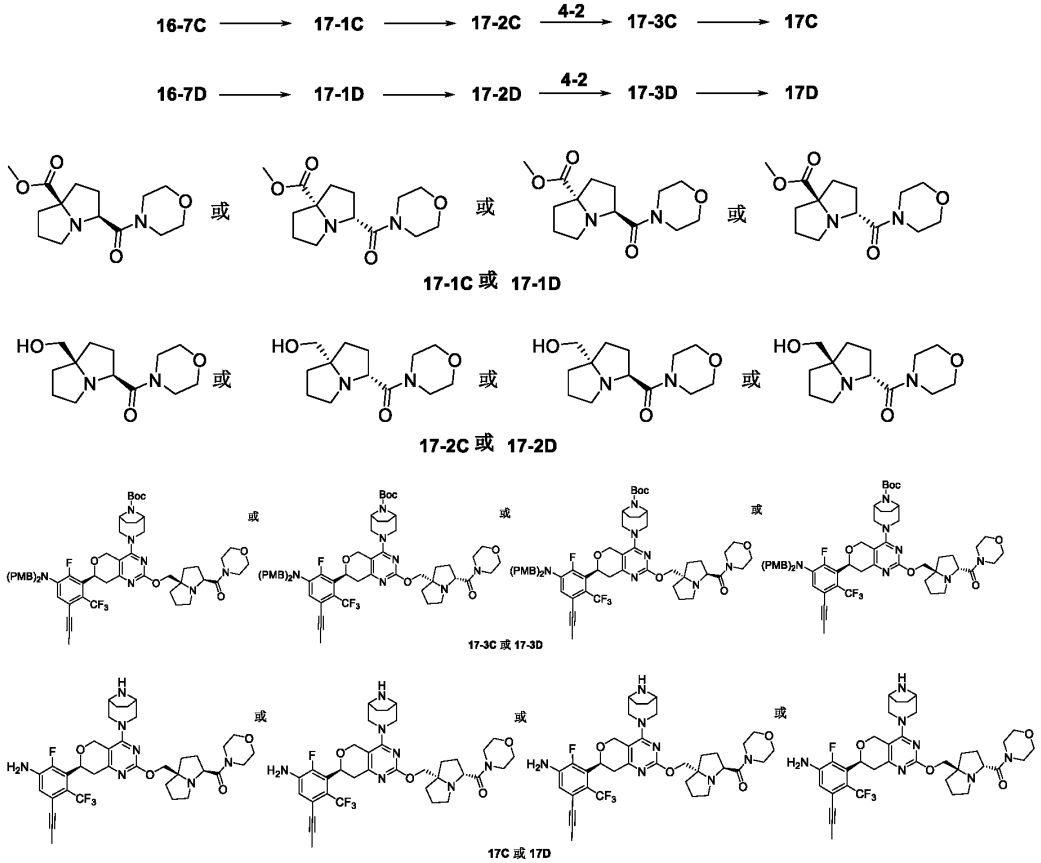
Step 11

Compound **16-10C** (0.20 g, 0.18 mmol) was added to trifluoroacetic acid (4 mL), and the solution was stirred and reacted at 60 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile): 55%-70%, lyophilized to obtain compound **16C**. MS m/z= 672.5$[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.16 - 5.14 (m, 1H), 4.81 - 4.78 (m, 1H), 4.67 - 4.63 (m, 1H), 4.16 - 4.13 (m, 2H), 4.09 - 4.08 (m, 1H), 3.75 - 3.72 (m, 1H), 3.54 - 3.51 (m, 3H), 3.43 - 3.40 (m, 1H), 3.28 - 3.17 (m, 3H), 3.06 - 3.03 (m, 1H), 2.91 - 2.83 (m, 2H), 2.78 - 2.72 (m, 1H), 2.12 - 2.08 (m, 2H), 2.02 - 1.91 (m, 11H), 1.76 - 1.66 (m, 2H), 1.14 (t, J = 8.0 Hz, 3H).

Compound **16-10D** (0.16 g, 0.14 mmol) was added to trifluoroacetic acid (4 mL), and the reaction was stirred and reacted at 60 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile): 55%-70%, lyophilized to obtain compound 16D. MS m/z= 672.5$[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0

Hz, 1H), 5.17 - 5.12 (m, 1H), 4.84 - 4.78 (m, 1H), 4.66 - 4.63 (m, 1H), 4.18 - 4.12 (m, 2H), 4.05 - 4.03 (m, 1H), 3.74 - 3.71 (m, 1H), 3.53 - 3.50 (m, 3H), 3.43 - 3.40 (m, 1H), 3.28 - 3.17 (m, 3H), 3.05 - 3.02 (m, 1H), 2.92 - 2.82 (m, 2H), 2.78 - 2.71 (m, 1H), 2.13 - 2.07 (m, 2H), 2.01-1.82 (m, 11H), 1.76 - 1.66 (m, 2H), 1.14 (t, J = 8.0 Hz, 3H)。

Example 17



Step 1

Compound **16-7C** (0.90 g, 4.22 mmol) was dissolved in N, N-dimethylformamide (10 mL) followed by addition of N, N-diisopropylethylamine (2.73 g, 21.10 mmol), N,N,N′,N′-tetramethyl-O-(7-azabenzotriazole-1-yl) hexafluorourea phosphate (3.21 g, 8.44 mmol), morpholine 735.43 mg, 8.44 mmol) and reaction at 25 °C for 12 hours. The reaction solution was added with water (10 mL), extracted with ethyl acetate (20 mL * 3), combined with the extracted organic phase, washed with saturated brine (10 mL), dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and column chromatography separated (dichloromethane: methanol = 20:1) to obtain compound **17-1C**. MS m/z = 283.2 $[M+H]^+$.

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material

to obtain compound **17-1D**. MS m/z = 283.2 $[M+H]^+$.

Step 2

Compound **17-1C** (20.00 mg, 70.84 μmol) was dissolved in methanol (0.5 mL), sodium methoxide (38.27 μg, 0.71 μmol) was added and sodium borohydride (8.04 mg, 212.51 μmol) at 0 °C, and reacted at 25 °C for 16 hours. The reaction was quenched by adding saturated ammonium chloride (10 mL), extracted with ethyl acetate (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain compound **17-2C**. MS m/z = 255.3 $[M+H]^+$.

With reference to step 2, compound **17-1C** was replaced with compound **17-1D** as the raw material to obtain compound **17-2D**. MS m/z = 255.3 $[M+H]^+$.

Step 3

Compound **17-2C** (66.00 mg, 259.51 μmol) was dissolved in tetrahydrofuran (10 mL), sodium hydrogen (31.14 mg, 1.30 mmol, 60% purity) was added at 0 °C, stirred for 0.5 hours, and compound **4-2** (228.36 mg, 259.51 μmol) was added at the end, and reacted at 25 °C for 2 hours. Add water (10 mL) to quench the reaction, extract with ethyl acetate (20 mL), dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure, and separate by column chromatography (petroleum ether: ethyl acetate = 0:1) to obtain compound **17-3C**. MS m/z = 1054.9 $[M+H]^+$.

With reference to step 3, compound **17-2C** was replaced with compound **17-2D** as the raw material to obtain compound **17-3D**. MS m/z = 1054.9 $[M+H]^+$.

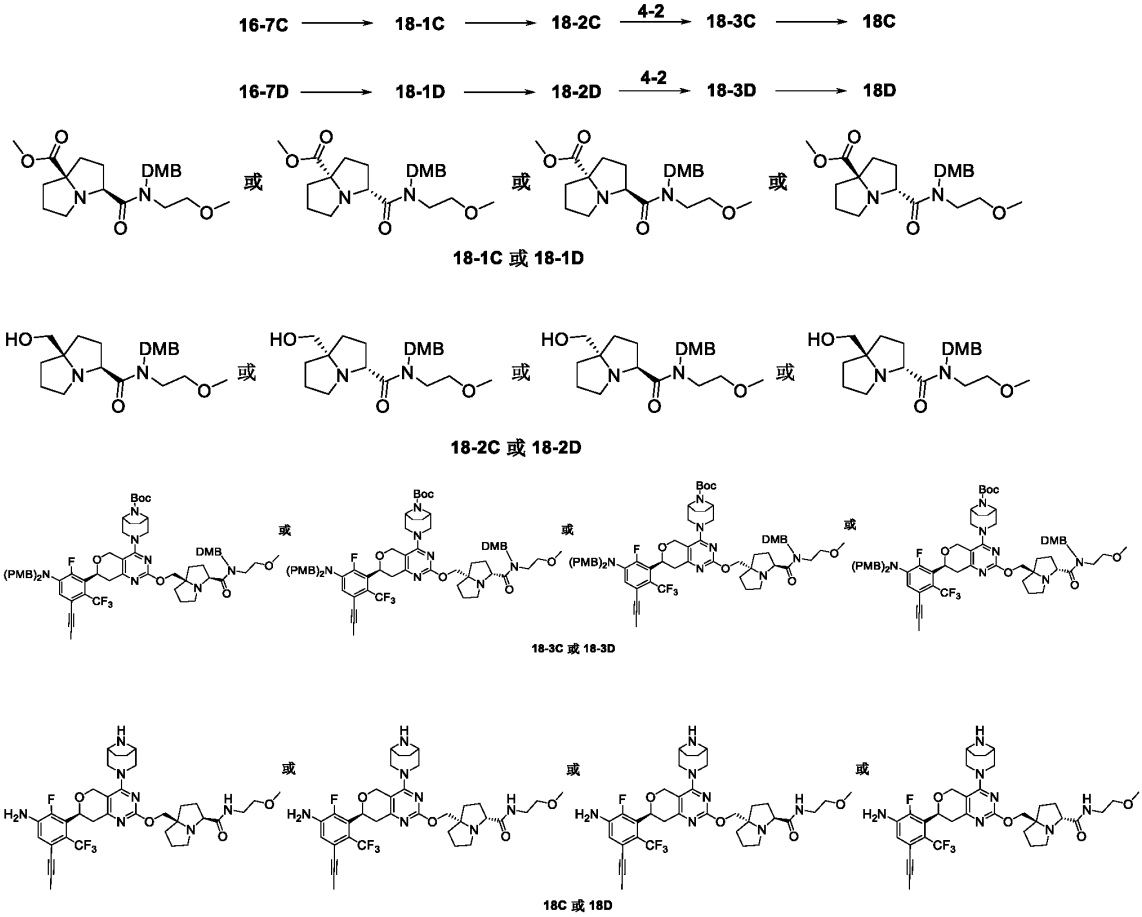
Step 4

Compound **17-3C** (0.20 g, 189.72 μmol) was dissolved in dichloromethane (4 mL), trifluoroacetic acid (2 mL) was added, and reacted at 25 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.1% formic acid) - acetonitrile]; gradient: (acetonitrile): 40%-75%. After lyophilization, the formate of compound **17C** was obtained. MS m/z= 714.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.29 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.18 (dd, J = 8.0, 4.0 Hz, 1H), 4.82 (s, 1H), 4.71 (d, J = 16.0 Hz, 1H), 4.30 - 4.22 (m, 3H), 4.12 (d, J = 12.0 Hz, 2H), 4.04 (dd, J = 12.0, 4.0 Hz, 1H), 3.78 - 3.57 (m, 9H), 3.52 - 3.46 (m, 1H), 3.25 (d, J = 12.0 Hz, 2H), 2.94 - 2.87 (m, 2H), 2.76 - 2.70 (m, 1H), 2.31 - 2.24 (m, 2H), 2.12 - 2.09 (m, 3H), 2.02 (s, 3H), 1.99 - 1.83 (m, 6H), 1.74 - 1.66 (m, 1H)。

Compound **17-3D** (0.10 g, 94.86 μmol) was dissolved in dichloromethane (2 mL), trifluoroacetic acid (1 mL) was added, and reacted at 25 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile

phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile): 55%-70%), lyophilized to obtain compound **17D**. MS m/z = 714.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0,4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.11 - 4.05 (m, 2H), 3.80 - 3.76 (m, 1H), 3.74 - 3.60 (m, 4H), 3.58 - 3.48 (m, 6H), 3.42 - 3.39 (m, 2H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.03 (d, *J* = 12 Hz, 1H), 2.87 - 2.76 (m, 2H), 2.58 - 2.52 (m, 1H), 2.22 - 2.11 (m, 1H), 2.01 - 1.98 (m, 5H), 1.94 - 1.88 (m, 1H), 1.85 - 1.80 (m, 4H), 1.79-1.66 (m, 3H), 1.61-1.54 (m, 1H).

Example 18



Step 1

Compound **16-7C** (0.15 g, 703.47 μmo l) was dissolved in dichloromethane (10 mL), N,N-diisopropylethylamine (3.52 mmol, 612.65 μL), N-(2,4-dimethoxybenzyl)-2-methoxyethanamine (316.96 mg, 1.41 mmol), N,N,N′,N′-tetramethyl-O-7-azabenzotriazole-1-yl hexafluorourea phosphate (534.96 mg, 1.41 mmol), and reacted at 25 °C for 1 hour. The organic phase was concentrated under reduced pressure and column chromatography separated (petroleum ether: ethyl

acetate = 3:1) to obtain compound **18-1C**. MS m/z =421.4 $[M+H]^+$.

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **18-1D**. MS m/z = 421.4 $[M+H]^+$.

Step 2

Compound **18-1C** (0.27 g, 642.10 μmo l) was dissolved in tetrahydrofuran (3 mL), sodium borohydride (485.84 mg, 12.84 mmol) and lithium chloride (27.22 mg, 642.10 μmol) were added, reacted at 50 °C for 16 hours. After cooling to room temperature, add water (3 mL) to quench the reaction, extract with ethyl acetate (5 mL * 3), combine the organic phases, concentrate under reduced pressure to obtain compound **18-2C**. MS m/z = 393.3 $[M+H]^+$.

With reference to step 2, compound **18-1C** was replaced with compound **18-1D** as the raw material to obtain compound **18-2D**. MS m/z = 393.3 $[M+H]^+$.

Step 3

Compound **18-2C** (0.18 g, 321.03 μmo l) was dissolved in tetrahydrofuran (5 mL) and then cooled to 0 °C. Sodium hydrogen (17.12 mg, 428.04 μmo l, 60% purity) was added, and the reaction was performed at 0 °C for 0.5 hours. Add **4-2** (188.33 mg, 214.02 μmo l), and react at 25 °C for 0.5 hour. Saturated aqueous ammonium chloride solution (15 mL) was quenched, extracted with ethyl acetate (5 mL * 3), the organic phase was combined and concentrated under reduced pressure, and column chromatography separated (petroleum ether: ethyl acetate = 1:1) to obtain compound **18-3C**. MS m/z = 1192.8 $[M+H]^+$.

With reference to step 3, compound **18-2C** was replaced with compound **18-2D** as the raw material to obtain compound **18-3D**. MS m/z = 1192.8 $[M+H]^+$.

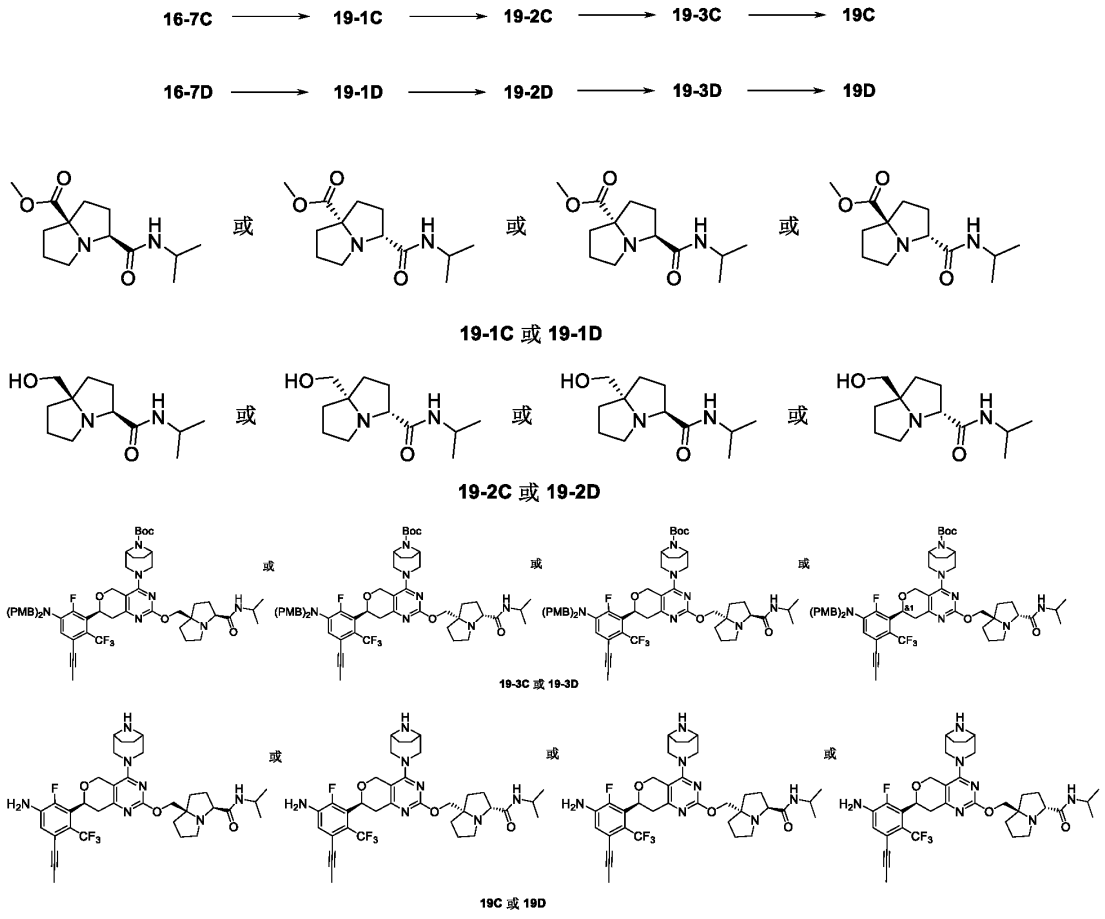
Step 4

Compounds **18-3C** (0.20 g, 167.74 μmol) were dissolved in trifluoroacetic acid (10 mL) and reacted at 50 °C for 0.5 hours. The organic phase was concentrated under reduced pressure to obtain the crude product, and the crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile): 55%-70%, and lyophilized to obtain compound **18C**. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.17 - 4.06 (m, 3H), 3.77 (dd, J = 8.0, 4.0 Hz, 1H), 3.53 (d, J = 12.0 Hz, 3H), 3.49 - 3.36 (m, 5H), 3.34 (s, 3H), 3.21 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.95 - 2.91 (m, 1H), 2.85 (dd, J = 16.0, 4.0 Hz, 1H), 2.78 - 2.69 (m, 1H), 2.13 - 2.06 (m, 2H), 2.04 - 1.96 (m, 5H), 1.94 - 1.89 (m, 4H), 1.85 - 1.82 (m, 2H), 1.76 - 1.66 (m, 2H).

Weigh compound **18-3D** (0.15 g, 125.80 μmo l), add dichloromethane (2.5 mL), add trifluoroacetic

acid (2.5 mL), and react at 25°C for 0.5 hour. The organic phase was concentrated under reduced pressure, and the crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia water) - acetonitrile]; gradient: (acetonitrile): 55%-70%. After lyophilization, compound **18D** was obtained. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.15 (t, *J* = 12.0 Hz, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.78 - 3.75 (m, 1H), 3.53 (d, *J* = 8.0 Hz, 3H), 3.49 - 3.36 (m, 5H), 3.34 (s, 3H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.90 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.76 - 2.70 (m, 1H), 2.15 - 2.07 (m, 2H), 2.01 - 1.94 (m, 5H),1.95 - 1.87 (m, 4H), 1.86 - 1.80 (m, 2H), 1.76-1.66 (m, 2H).

Example 19



Step 1

Weigh compound **16-7C** (0.40 g, 1.86 mol), add with dichloromethane (6 mL), isopropylamine (166.33 mg, 2.81 mmol), 2-(7-azabenzotriazole)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (1.43 g, 3.75 mmol), and N, N-diisopropylethylamine (0.73 g, 5.63 mol) for reacting at 25 °C for 3 hours. Add water (10 mL), dichloromethane (10 mL * 3) forextraction, and concentrate the organic phase under reduced pressure to obtain compound **19-1C**, MS m/z = 255.0 $[M+H]^+$.

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **19-1D**. MS m/z = 255.0 $[M+H]^+$.

Step 2

Weigh compound **19-1C** (0.10 g, 0.39 mmol), add anhydrous tetrahydrofuran (3 mL) solution under nitrogen protection, cool to 0 °C, add tetrahydrofuran solution of lithium tetrahydroaluminum (1.18 mmol, 0.47 ml, 2.5 M), and react at 25 °C for 15 minutes. Add 0.2 mL of water to the reaction solution at 0 °C, add 0.2 mL of 15% NaOH solution to quench the reaction, stir for 10 minutes, filter the reaction solution, wash the filter cake with 5 mL of tetrahydrofuran, and concentrate the filtrate to obtain compound **19-2C**, MS m/z = 227.1 $[M+H]^+$

With reference to step 2, compound **19-1C** was replaced with compound **19-1D** as the raw material to obtain compound **19-2D**. MS m/z = 227.1 $[M+H]^+$.

Step 3

Weigh compound **19-2C** (50.0 mg, 0.22 mmol), add anhydrous tetrahydrofuran (5 mL), add sodium hydride (15.91 mg, 0.66 mmol, 60%) under ice bath at 0 °C, stir at 25 °C for 30 minutes, and add compound **4-2** (0.20 g, 0.22 mmol), and react at 25 °C for 1 hour. Add water (5 mL) to quench the reaction solution, extract with ethyl acetate (5 mL*3), concentrate the organic phase under reduced pressure, and separate by column chromatography (dichloromethane: methanol = 20:1) to obtain compound **19-3C**, MS m/z = 1026.8 $[M+H]^+$.

With reference to step 3, compound **19-2C** was replaced with compound **19-2D** as the raw material to obtain compound **19-3D**. MS m/z = 1026.8 $[M+H]^+$.

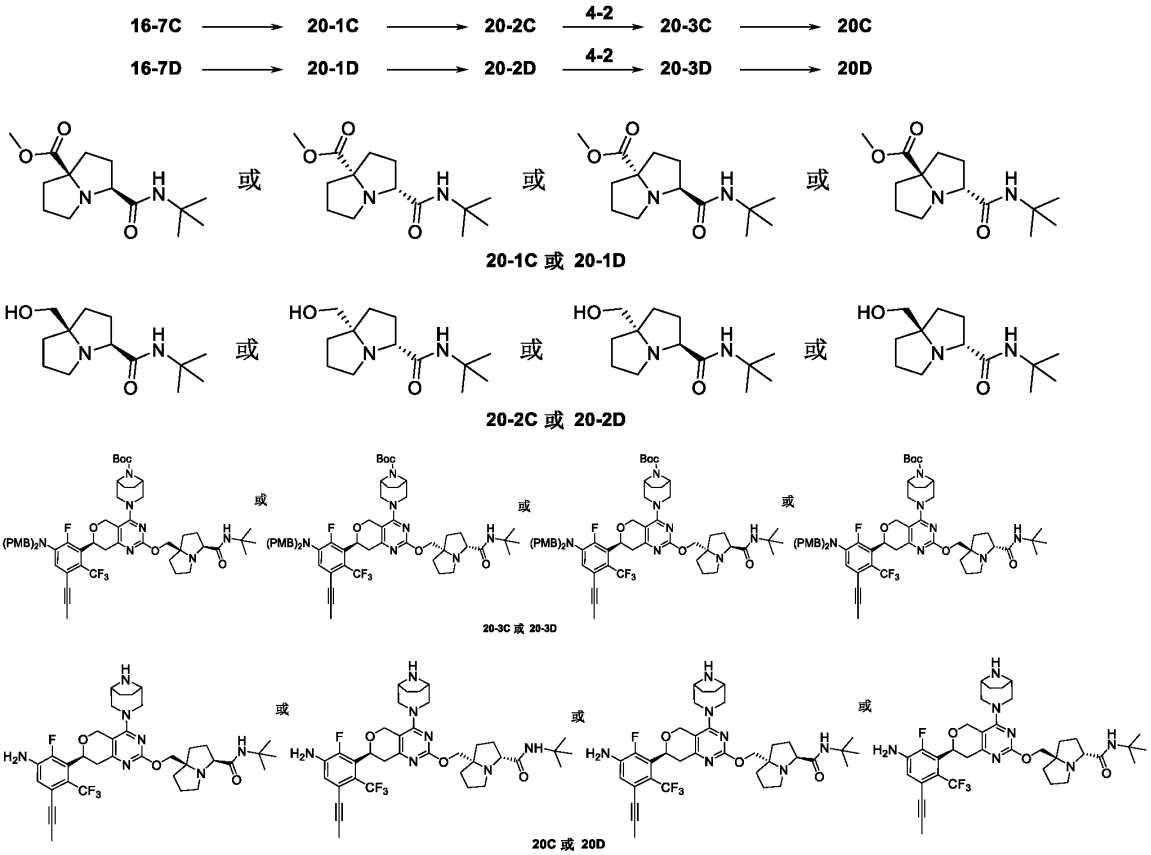
Step 4

Compound **19-3C** (50 mg, 0.05 mmol) was dissolved in dichloromethane (2 mL), to which trifluoroacetic acid (1 mL) was added, and the reaction solution was reacted at 25 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.05% formic acid)-acetonitrile]; acetonitrile: 45%-75%. After lyophilization, the formate of compound **19C** was obtained. MS m/z = 686.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.45 (s, 1.52 H), 6.91 (d, J = 8.4 Hz, 1 H), 5.20 - 5.16 (m, 1 H), 4.84 - 4.79 (m, 1 H), 4.70 (d, J = 13.7 Hz, 1 H), 4.33 (d, J = 11.2 Hz, 1 H), 4.26 - 4.10 (m, 2 H), 4.08 - 3.97 (m, 4 H), 3.76 - 3.73 (m, 1 H), 3.58 (d, J = 13.4 Hz, 1 H), 3.27 - 3.21 (m, 3

H), 3.03 - 3.01 (m, 1 H), 2.93 - 2.88 (m, 1 H), 2.26 - 2.06 (m, 8 H), 2.01 - 1.94 (m, 5 H), 1.92 - 1.87 (m, 2 H), 1.17 (dd, *J* = 6.6, 1.5 Hz, 6 H)。

Compound **19-3D** (50 mg, 0.05 mmol) was dissolved in dichloromethane (2 mL), to which trifluoroacetic acid (1 mL) was added, and the reaction solution was reacted at 25 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.05% formic acid)-acetonitrile]; acetonitrile: 45%-75%. After lyophilization, compound **19D** formate was obtained. MS m/z = 686.5[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.36 (s, 1.59 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.10 - 5.07 (m, 1 H), 4.81 - 4.78 (m, 1 H), 4.61 (d, *J* = 13.6 Hz, 1 H), 4.22 - 4.08 (m, 3 H), 3.94 - 3.88 (m, 4 H), 3.63 (d, *J* = 13.6 Hz, 1 H), 3.48 (d, *J* = 13.2 Hz, 1 H), 3.17 - 3.03 (m, 3 H), 2.91 - 2.78 (m, 2 H), 2.15 - 1.99 (m, 6 H), 1.98 - 1.92 (m, 6 H), 1.84 - 1.76 (m, 3 H), 1.07 (d, *J* = 6.6 Hz, 6 H)。

Example 20



Step 1

Compound **16-7C** (100 mg, 468.98 μmol) was dissolved in N,N-dimethylformamide (2 mL), 2-

chloro-1-methylpyridine iodide (179.72 mg, 703.47 μmol), triethylamine (142.37 mg, 1.41 mmol), tert-butylamine (51.45 mg, 703.47 μmol) was added and reacted at 25 °C for 2 hours. Add water (10 mL), extract with ethyl acetate (10 mL * 3), combine the extracted organic phases, wash with saturated brine (10 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography separation (petroleum ether: ethyl acetate = 1:1) yielded compound **20-1C**. MS m/z = 269.0 $[M+H]^+$.

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **20-1D**. MS m/z = 269.0 $[M+H]^+$.

Step 2

Compound **20-1C** (300 mg, 1.12 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL), cooled to 0 °C under nitrogen protection, and lithium borohydride in tetrahydrofuran solution (1.12 mL, 2 M) was added dropwise, and heated to 50 °C for stirring and reacting for 8 hours. Add 3 mL of water to quench the reaction, filter, and concentrate the filtrate under reduced pressure to obtain the crude product. The crude product was separated by column chromatography (dichloromethane: methanol = 10:1) to obtain compound **20-2C**. MS m/z = 241.1$[M+H]^+$.

With reference to step 2, compound **20-1C** was replaced with compound **20-1D** as the raw material to obtain compound **20-2D**. MS m/z = 241.1 $[M+H]^+$.

Step 3

Compound **20-2C** (81.90 mg, 340.93 μmol) was dissolved in anhydrous tetrahydrofuran (5 mL), cooled to 0 °C, and sodium hydride (20.50 mg, 853.75 μmol, 60% purity) was slowly added therein, and then heated to 25 °C for stirring and reaction for 0.5 hours. Compound **4-2** (200 mg, 227.28 μmol) was added and reacted at 25°C for 2 hours. Add 3 mL of water to quench the reaction, extract with ethyl acetate ((5mL*3), combine the extracted organic phases, wash with saturated brine (10 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography (petroleum ether: ethyl acetate = 1:1) yielded compound **20-3C**. MS m/z = 1040.8 $[M+H]^+$.

With reference to step 3, compound **20-2C** was replaced with compound **20-2D** as the raw material to obtain compound **20-3D**. MS m/z = 1040.8 $[M+H]^+$.

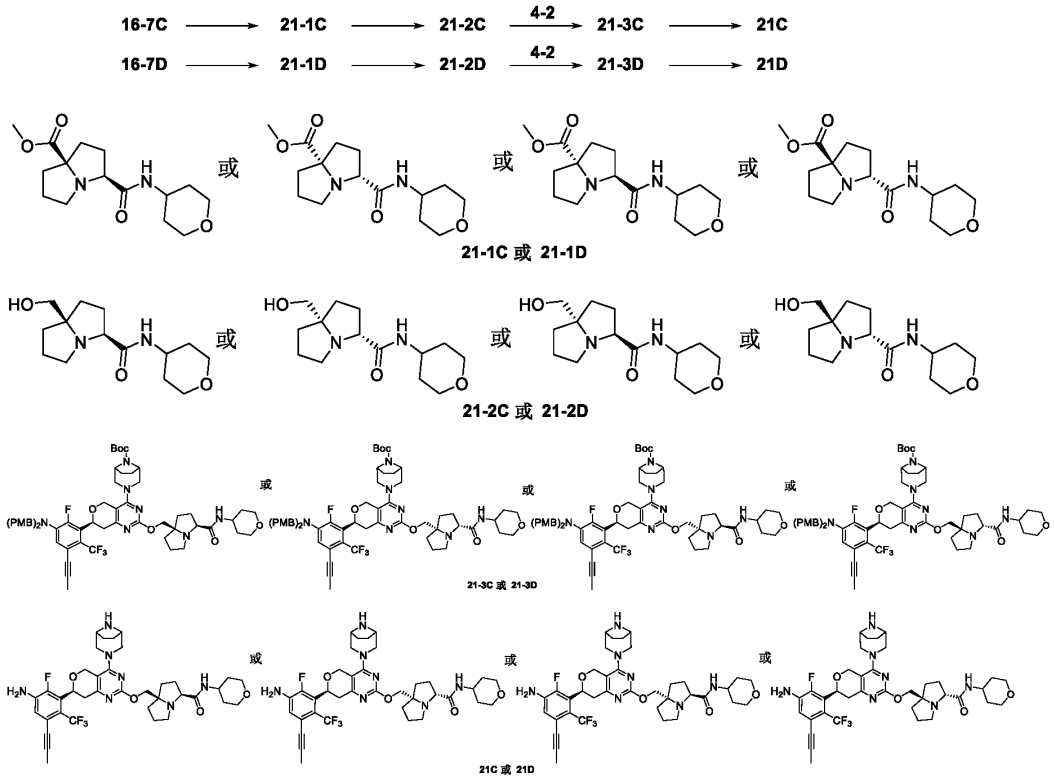
Step 4

Compounds **20-3C** (100 mg, 96.14 μmol) were dissolved in anhydrous methylene chloride (3 mL), to which trifluoroacetic acid (1 mL) was added, and the reaction solution was reacted at 25 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography (column: Xtimate C18 150*40 mm*5 μm; mobile phase: [water (0.05% formic acid)-acetonitrile]; (acetonitrile): 10%-40 %);

after lyophilization, the formate of compound 20C was obtained.**20C** MS m/z = 700.6 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.20 - 5.15 (m, 1H), 4.82 (d, *J* = 13.6 Hz, 1H), 4.69 (d, *J* = 13.6 Hz, 1H), 4.27 - 4.14 (m, 3H), 3.88 (s, 3H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.28 - 3.15 (m, 2H), 3.10 - 3.04 (m, 1H), 2.95 - 2.86 (m, 2H), 2.21 - 2.12 (m, 3H), 2.02 - 1.76 (m, 12H), 1.36 (s, 9H).

Compound **20-3D** (150 mg, 144.21 μmol) was dissolved in methylene chloride (4.5 mL), and then trifluoroacetic acid (1.5 mL) was added to the reaction solution, which was reacted at 25 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared by high performance liquid chromatography separation (column: Xtimate C18 150 * 40 mm * 5 μm; mobile phase: [water (0.1% ammonium bicarbonate) - acetonitrile] ; 35% - 53%. After lyophilization, compound 20D was obtained.**20D** MS m/z = 700.6 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.4 Hz, 1H), 5.17 - 5.12 (m, 1H), 4.80 (d, *J* = 13.6 Hz, 1H), 4.65 (d, *J* = 13.6 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.71 - 3.68 (m, 1H), 3.54 - 3.51 (m, 3H), 3.43 - 3.40 (m, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.93 - 2.71 (m, 3H), 2.14 - 2.09 (m, 2H), 2.06 - 2.01 (m, 4H), 1.92-1.83 (m, 7H), 1.74 - 1.96 (m, 2H), 1.35 (s, 9H)。

Example 21



Step 1

Compound **16-7C** (150 mg, 703.47 μmol) was dissolved in N,N-dimethylformamide (2 mL), 4-aminotetrahydrofuran (106.73 mg, 1.06 mmol), N-methylimidazole (173.27 mg, 2.11 μmol), tetramethyl chlorourea hexafluorophosphate (296.07 mg, 1.06 mmol) was added and reacted at 25 °C for 3 hours. Add water (10 mL), extract with ethyl acetate (10 mL * 3), combine the extracted organic phases, wash with saturated brine (5 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography separation (dichloromethane: methanol = 20:1) yielded compound **21-1C**. MS m/z = 297.1 $[M+H]^+$.

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **21-1D**. MS m/z = 297.1 $[M+H]^+$.

Step 2

Compound **21-1C** (300 mg, 1.01 mmol) was dissolved in anhydrous methanol (5 mL), sodium methanol (21.90 mg, 404.91 μmol) and sodium borohydride (191.50 mg, 5.06 mmol) were added, and reacted at 50 °C for 24 hours. Add 3 mL saturated ammonium chloride aqueous solution to quench reaction, filter, and filtrate concentration under reduced pressure to obtain crude product Column chromatography separation (dichloromethane: methanol = 10:1) yielded compound **21-2C**. MS m/z = 269.2 268.5 $[M+H]^+$.

With reference to step 2, compound **21-1C** was replaced with compound **21-1D** as the raw material to obtain compound **21-2D**. MS m/z =269.2 $[M+H]^+$.

Step 3

Compound **21-2C** (100 mg, 372.65 μmol) was dissolved in anhydrous tetrahydrofuran (5 mL), cooled to 0 °C, and sodium hydride (44.70 mg, 1.12 mmol, 60% purity) was slowly added to it, and the temperature was increased to 25 °C for stirring and reaction for 0.5 hours. Compound **4-2** (163.90 mg, 186.32 μmol) was added and reacted at 25 °C for 2 hours. Add 3 mL of water to quench the reaction, extract with ethyl acetate (5 mL*3), combine the extracted organic phases, wash with saturated brine (10 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography (dichloromethane: methanol = 20:1) yielded compound **21-3C**. MS m/z = 1068.5 $[M+H]^+$.

With reference to step 3, compound **21-2C** was replaced with compound **21-2D** as the raw material to obtain compound **21-3D**. MS m/z = 1068.5 $[M+H]^+$.

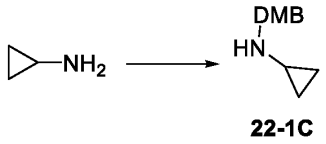
Step 4

Compounds **21-3C** (114 mg, 106.72 μmol) were dissolved in anhydrous dichloromethane (0.9 mL), to which trifluoroacetic acid (0.3 mL) was added and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared by

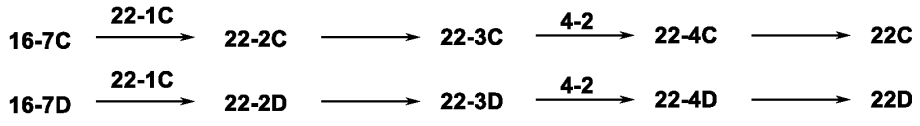
high performance liquid chromatography separation (column: Xtimate C18 150 * 40 mm * 5 μm; mobile phase: [water (0.05% formic acid) - acetonitrile]; acetonitrile]: 10% - 60%). After lyophilization, the formate of compound 21C is obtained.**21C** MS m/z = 728.5 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.22 (s, 1.38H), 7.97 (d, J = 7.7 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.02 (s, 2H), 5.05 - 5.01 (m, 1H), 4.75 (d, J = 13.7 Hz, 1H), 4.57 (d, J = 13.7 Hz, 1H), 3.94 - 3.90 (m, 3H), 3.83 - 3.79 (m, 3H), 3.64 (s, 2H), 3.54 - 3.51 (m, 1H), 3.44 - 3.41 (m, 1H), 3.35 - 3.30 (m, 4H), 3.09 - 3.02 (m, 1H), 2.98 (d, J = 12.5 Hz, 1H), 2.82 - 2.77 (m, 1H), 2.75 - 2.70 (m, 1H), 2.66 - 2.59 (m, 1H), 2.03 (s, 3H), 1.97 - 1.80 (m, 6H), 1.80 - 1.52 (m, 8H), 1.47 - 1.37 (m, 2H).

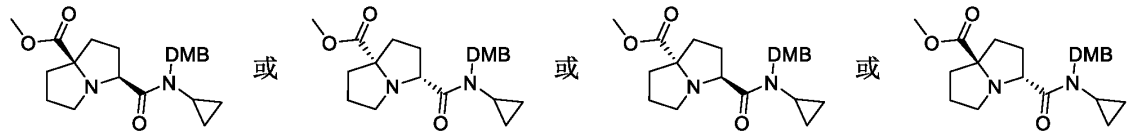
Compounds **21-3D** (200 mg, 187.23 μmol) were dissolved in anhydrous dichloromethane (5 mL), to which trifluoroacetic acid (5 mL) was added and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared by high performance liquid chromatography (column: Xtimate C18 150*40mm*5μm; mobile phase: [water (0.05% formic acid)-acetonitrile]; acetonitrile]; 10%-60 %). After lyophilization, the formate of compound 21D was obtained.**21D** MS m/z = 728.5 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.14 (s, 0.56H), 7.96 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.01 (s, 2H), 5.04 - 5.00 (m, 1H), 4.74 (d, J = 13.7 Hz, 1H), 4.54 (d, J = 13.7 Hz, 1H), 4.05 - 3.92 (m, 4H), 3.85 - 3.79 (m, 4H), 3.64 - 3.51 (m, 2H), 3.46 (d, J = 13.3 Hz, 1H), 3.40 - 3.35 (m, 3H), 3.14 - 3.06 (m, 2H), 2.87 - 2.68 (m, 2H), 2.67 - 2.52 (m, 1H), 2.03 (s, 3H), 1.91 - 1.53 (m, 14H), 1.46 - 1.38 (m, 2H)。

Example 22

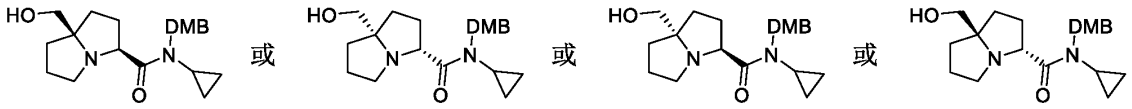


22-1C

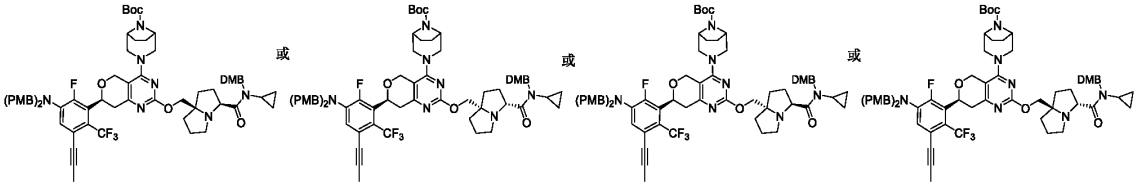




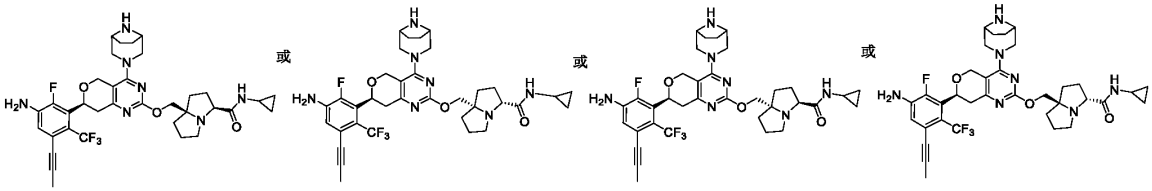
22-2C 或 22-2D



22-3C 或 22-3D



22-4C 或 22-4D



22C 或 22D

Step 1

Add 2,4-dimethoxybenzaldehyde (500 mg, 3.01 mmol) to anhydrous tetrahydrofuran (5 mL), add cyclopropylamine (6.02 mmol, 416.97 μL) and glacial acetic acid (18.00 mg, 300.89 μmol), and react at 25 °C for 2 hours. Sodium borohydride (567.20 mg, 9.03 mmol) was added to the above system and stirred and reacted at 25 °C for 16 hours. Water (5 mL) was added for quenching, dichloromethane (10 mL * 3) was extracted, the extracted organic phase was combined, washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to obtain compound **22-1C**. MS m/z = 208.2 $[M+H]^+$.

Step 2

Compound **16-7C** (140 mg, 656.56 μmol) was dissolved in anhydrous dichloromethane (6 mL), N,N-diisopropylethylamine (3.28 mmol, 571.80 μL) was added, compound **22-1C** (176.90 mg, 853.54 mmol), N,N,N′,N′-tetramethyl-O-(7-azabenzotriazole-1-yl) hexafluorourea phosphate (499.31 mg, 1313.14 μmol) was added, reacted at 25 °C for 16 hours. Water (5 mL) was added for quenching, extracted with ethyl acetate (10 mL * 3), the extracted organic phase was combined, washed with saturated brine (10 mL), dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and column chromatography separation was performed (petroleum ether: ethyl acetate = 3:1) to obtain compound **22-2C**. MS m/z = 403.2 $[M+H]^+$.

With reference to step 2, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **22-2D**. MS m/z = 403.2 $[M+H]^+$.

Step 3

Compound **22-2C** (170 mg, 422.38 μmo l) was dissolved in anhydrous tetrahydrofuran (3 mL) and anhydrous methanol (3 mL), sodium borohydride (79.90 mg, 2.11 mmo l) was added, lithium chloride (17.90 mg, 422.38 μmo l) was reacted at 50 °C for 2 hours. Add water (0.5 mL) to quench, filter, and concentrate the filtrate under reduced pressure to obtain compound **22-3C**. MS m/z =375.2 $[M+H]^+$.

With reference to step 3, compound **22-2C** was replaced with compound **22-2D** as the raw material to obtain compound **22-3D**. MS m/z = 375.2 $[M+H]^+$.

Step 4

Compound **22-3C** (104 mg, 277.72 μmol) was dissolved in anhydrous tetrahydrofuran (5 mL), sodium hydride (33.30 mg, 833.17 μmol, 60% purity) was added, and the reaction was performed at 0 °C for 0.5 hours. Compound **4-2** (150.00 mg, 170.46 μmo l) was added and reacted at 25 °C for 1 hour. Add saturated aqueous ammonium chloride solution (10 mL) for quenching, extract with ethyl acetate (10 mL * 3), combine the extracted organic phases, wash with saturated brine (10 mL), dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure, and separate by column chromatography (petroleum ether: Ethyl acetate = 1:1) to obtain compound **22-4C**. MS m/z = 1174.5 $[M+H]^+$.

With reference to step 4, compound **22-3C** was replaced with compound **22-3D** as the raw material to obtain compound **22-4D**. MS m/z = 1174.5 $[M+H]^+$.

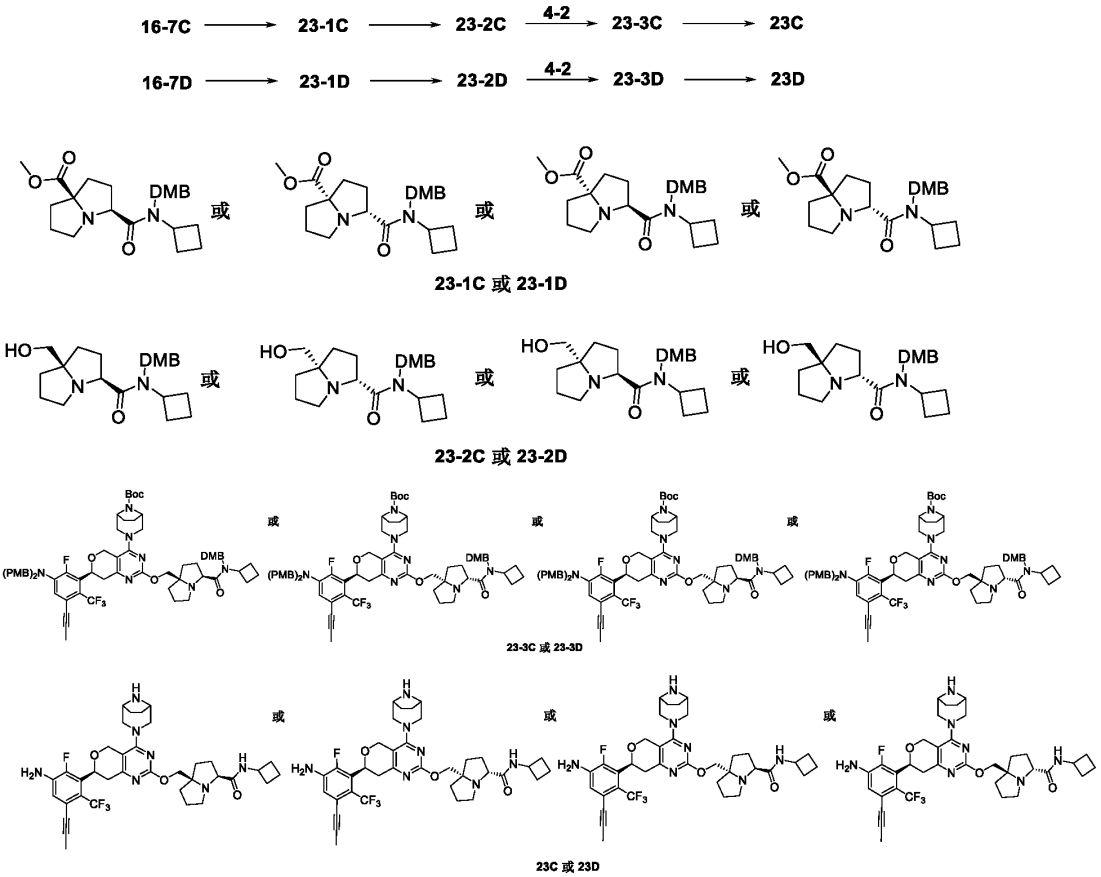
Step 5

Compounds **22-4C** (150.00 mg, 127.73 μmo l) were dissolved in trifluoroacetic acid (5 mL) and reacted at 50 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (column: Xtimate C18 150*40mm*5μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile): 35%-60%, and lyophilized to obtain compound **22C**. MS m/z = 684.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.4 Hz, 1H), 5.14 (dd, J = 11.6 Hz, 4.8 Hz, 1H), 4.79 (d, J = 13.6 Hz, 1H), 4.64 (d, J = 13.6 Hz, 1H), 4.14 - 4.04 (m, 3H), 3.68 (dd, J = 8.0 Hz, 5.2 Hz, 1H), 3.52 - 3.49 (m, 3H), 3.42 - 3.38 (m, 1H), 3.21 (dd, J = 17.6 Hz, 11.2 Hz, 1H), 3.03 (d, J = 12.4 Hz, 1H), 2.88 - 2.84 (m, 2H), 2.73 - 2.65 (m, 2H), 2.11 - 2.05 (m, 2H), 2.01 - 1.97 (m, 5H), 1.94 - 1.81 (m, 6H), 1.76 - 1.64 (m, 2H), 0.75 - 0.71 (m, 2H), 0.53 - 0.48 (m, 2H).

Compounds **22-4D** (100.00 mg, 85.16 μmo l) were dissolved in trifluoroacetic acid (3 mL) and reacted at 50 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography

separation (chromatographic column: Xtimate C18 150*40mm*5μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; gradient: (acetonitrile: 35%-70%, and lyophilized to obtain compound **22D**. MS m/z = 684.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.4 Hz, 1H), 5.14 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.79 (d, *J* = 13.6 Hz, 1H), 4.64 (d, *J* = 13.6 Hz, 1H), 4.16 - 4.12 (m, 2H), 4.03 (d, *J* = 10.4 Hz, 1H), 3.68 (dd, *J* = 8.0 Hz, 5.2 Hz, 1H), 3.53 - 3.50 (m, 3H), 3.42 - 3.39 (m, 1H), 3.21 (dd, *J* = 17.6 Hz, 11.2 Hz, 1H), 3.03 (d, *J* = 12.4 Hz, 1H), 2.88 - 2.81 (m, 2H), 2.78 - 2.66 (m, 2H), 2.12 - 2.06 (m, 2H), 2.01 - 1.97 (m, 5H), 1.95 - 1.81 (m, 6H), 1.77 - 1.66 (m, 2H), 0.76 - 0.72 (m, 2H), 0.52 - 0.48 (m, 2H).

Example 23



Step 1

Compound **16-7C** (0.20 g, 937.96 μmol) was dissolved in dimethylformamide (2 mL), followed by addition of N,N-diisopropylethylamine (606.12 mg, 4.69 mmol), N,N,N′,N′-tetramethyl-O-(7-azabenzotriazole-1-yl) hexafluorourea phosphate (713.28 mg, 1.88 mmol), N-[(2,4-dimethoxyphenyl) methyl]cyclobutamine 207.56 mg, 937.96 μmol), and reacted at 25 °C for 12 hours. The reaction solution was added to water (10 mL), extracted with ethyl acetate (20 mL * 3), concentrated under

reduced pressure, and column chromatography separated (petroleum ether: ethyl acetate = 5:1) to obtain compound **23-1C**. MS m/z = 417.4 $[M+H]^+$

With reference to step 1, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **23-1D**. MS m/z = 417.4 $[M+H]^+$.

Step 2

Compound **23-1C** (0.20 g, 480.18 μmol) was dissolved in methanol (2 mL), sodium methoxide (2.59 mg, 48.02 μmol) and boron-hydrogenated sodium (90.83 mg, 2.40 mmol) were added at 0 °C, and reacted at 25 °C for 16 hours. The reaction was quenched by adding saturated ammonium chloride (10 mL), extracted with ethyl acetate (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain compound **23-2C**. MS m/z = 389.3 $[M+H]^+$

With reference to step 2, compound **23-1C** was replaced with compound **23-1D** as the raw material to obtain compound **23-2D**. MS m/z = 389.3 $[M+H]^+$.

Step 3

Compound **23-2C** (50.00 mg, 128.70 μmol) was dissolved in tetrahydrofuran (1 mL), sodium hydrogen (51.48 mg, 1.29 mmol, 60% purity) was added at 0 °C, stirred for 0.5 hours, and compound **4-2** (113.25 mg, 128.70 μmol) was finally added, and reacted at 25 °C for 2 hours. The reaction was quenched by adding water (10 mL), extracted with ethyl acetate (20 mL), concentrated under reduced pressure, and separated by column chromatography (petroleum ether: ethyl acetate = 0:1) to obtain compound **23-3C**. MS m/z = 1188.7 $[M+H]^+$.

With reference to step 3, compound **23-2C** was replaced with compound **23-2D** as the raw material to obtain compound **23-3D**. MS m/z = 1188.7 $[M+H]^+$.

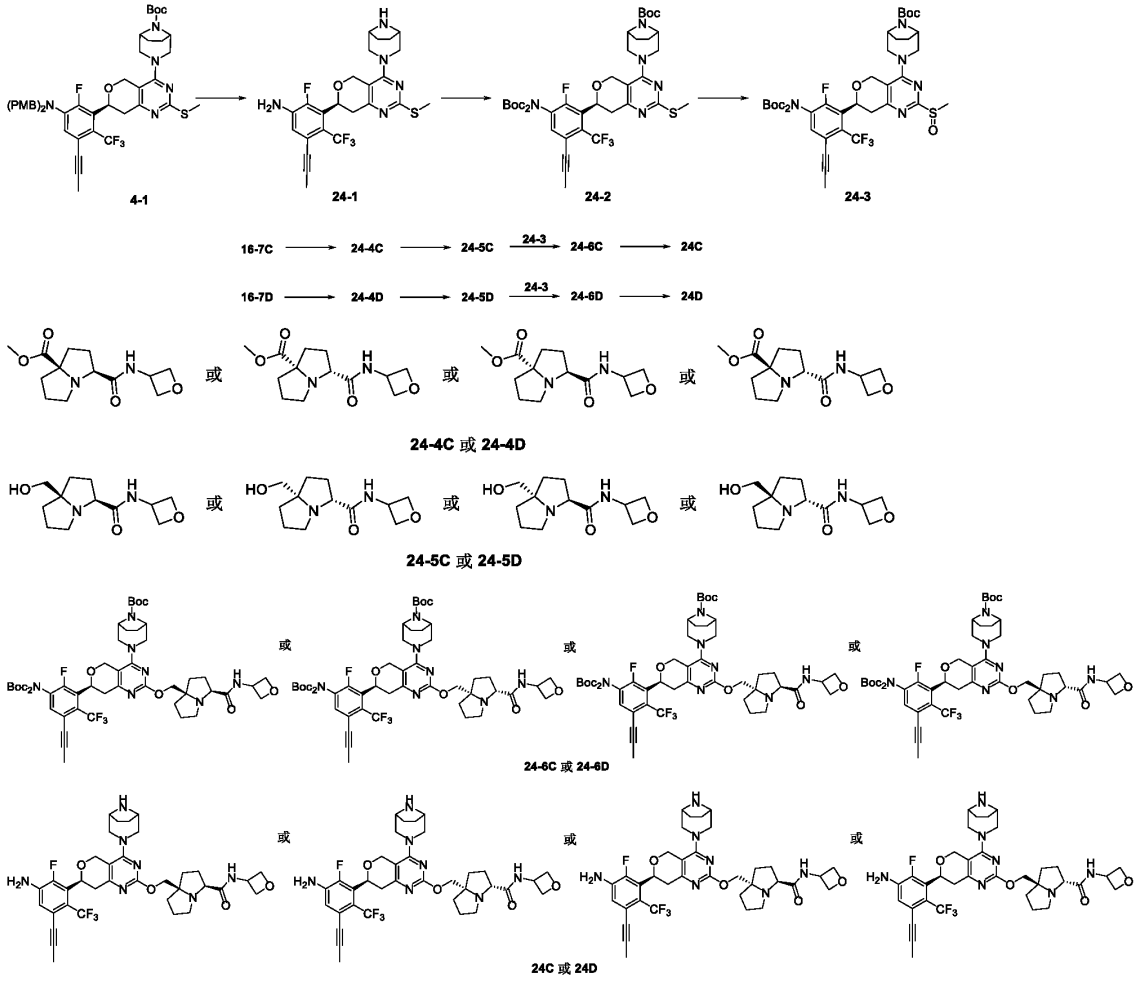
Step 4

Compounds **23-3C** (17 mg, 14.31 μmol) were dissolved in methylene chloride (1 mL), trifluoroacetic acid (0.3 mL) was added, and reacted at 25 °C for 0.5 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia)-acetonitrile]; gradient: (acetonitrile): 55%-70%, lyophilized to obtain compound **23C**. MS m/z= 698.5$[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.84 - 4.79 (m, 1H), 4.62 (d, *J* = 16.0 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.16 - 4.06 (m, 3H), 3.74 - 3.70 (m, 1H), 3.51 - 3.48 (m, 3H), 3.44 - 3.41 (m, 1H), 3.25 - 3.13 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.89 - 2.82 (m, 2H), 2.76 - 2.70 (m, 1H), 2.32 - 2.26 (m, 2H), 2.12 - 2.06 (m, 2H), 2.04 - 1.89 (m, 11H), 1.85 - 1.83 (m, 2H), 1.77 - 1.71 (m, 4H)。

Compound **23-3D** (40 mg, 33.66 μmol) was dissolved in methylene chloride (1 mL), trifluoroacetic acid (1 mL) was added, and the solution was stirred and reacted at 25 °C for 0.5 hour. The reaction

solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (Waters Xbridge, 250*19mm, 5mm; mobile phase: [water (0.1% ammonia)-acetonitrile]; gradient: (acetonitrile): 55%-70%). After lyophilization, compound **23D** was obtained. MS m/z= 698.5[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.83 - 4.78 (m, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.18 - 4.12 (m, 2H), 4.04 (d, J = 8.0 Hz, 1 H), 3.73 - 3.69 (m, 1H), 3.53 (d, J = 12.0 Hz, 3H), 3.43 - 3.41 (d, J = 8.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.91 - 2.82 (m, 2H), 2.76-2.70 (m, 1H), 2.33 - 2.26 (m, 2H), 2.11 - 2.07 (m, 2H), 2.01 - 1.90 (m, 11H), 1.85 - 1.83 (m, 2H), 1.78-1.68 (m, 4H).

Example 24



Step 1

Compound **4-1** (280 mg, 0.33 mmol) was dissolved in dichloromethane (3 mL), and then

trifluoroacetic acid (376 mg, 3.30 mmol) was added. The resulting reaction solution was stirred for 3 hours at 25 °C under nitrogen protection. The reaction solution was concentrated under reduced pressure, ethyl acetate 3 mL was added to the residue, and then hydrogen chloride/ethyl acetate solution (4M, 1 mL) was added to it, and the reaction was stirred at 25 °C for 1 hour, and concentrated under reduced pressure to obtain the hydrochloride salt of compound **24-1**.

Step 2

The hydrochloride salt of compound **24-1** (160 mg), triethylamine (159.50 mg, 1.58 mol) was added to dichloromethane (5 mL), then di-tert-butyl dicarbonate ester (1.38 g, 6.30 mmol) and 4-dimethylaminopyridine (38.51 mg, 0.33 mmol) were added, and the reaction solution was stirred for 12 hours under nitrogen protection at 25 °C. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to obtain compound **24-2**. MS m/z = 808.6 $[M+H]^+$.

Step 3

Compound **24-2** (240 mg, 0.30 mmol) was dissolved in tetrahydrofuran (5 mL), and then metachloroperoxybenzoic acid (61.52 mg, 0.35 mmol, 85% purity) was added. The obtained reaction solution was stirred and reacted at 25°C for 0.5 hours under nitrogen protection. The reaction solution was concentrated under reduced pressure to obtain compound **24-3**. MS m/z = 824.5 $[M+H]^+$.

Step 4

Compound **16-7C** (180 mg, 0.84 mmol) was dissolved in N,N-dimethylformamide (4 mL), benzotriazazole-N,N',N',N'-tetramethyl-uronium-hexafluorophosphate (641.95 mg, 1.69 mmol) and N,N-diisopropylethylamine (218.42 mg, 1.69 mmol) were added, and the reaction mixture was stirred at 25 °C for 30 minutes. In the above mixture, it was added oxetan-3-amine hydrochloride (92.09 mg, 1.26 mmol) and the resulting mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL), the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 20:1) yielded compound **24-4C**. MS m/z = 269.18 $[M+H]^+$.

With reference to step 4, compound **16-7C** was replaced with compound **16-7D** as the raw material to obtain compound **24-4D**. MS m/z = 269.18 $[M+H]^+$.

Step 5

Compounds **24-4C** (100 mg, 0.37 mmol) were dissolved in tetrahydrofuran (5 mL), sodium borohydride (69.98 mg, 1.85 mmol) and lithium chloride (78.42 mg, 1.85 mmol) were added, and reacted at 25°C for 12 hours under nitrogen protection. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL), the organic phase was washed with saturated brine,

dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 10:1) yielded compound **24-5C**. MS m/z = 241.22 $[M+H]^+$.

With reference to step 5, compound **24-4D** was replaced with compound **24-4C** as the raw material to obtain compound **24-5D**. MS m/z = 241.22 $[M+H]^+$.

Step 6

Compound **24-5C** (70 mg, 0.29 mmol) was dissolved in tetrahydrofuran (3 mL), followed by sodium hydrogen (12 mg, 0.29 mmol, 60% purity) under nitrogen protection, and the reaction was stirred at 25 °C for 0.5 hours, and then a solution of compound **24-3**(210 mg, 0.29 mmol) in tetrahydrofuran (1 mL) was added to the solution, and the reaction was stirred at 25 °C for 2 hours. The reaction solution was dissolved in 10 mL of ethyl acetate, then washed with saturated brine (5 mL), the organic phase was dried, then filtered and the filtrate was concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 20:1) yielded compound **24-6C**. MS m/z = 900.6 $[M-100+1]^+$.

With reference to step 6, compound **24-5C** was replaced with compound **24-5D** as the raw material to obtain compound **24-6D**. MS m/z = 900.6 $[M-100+1]^+$.

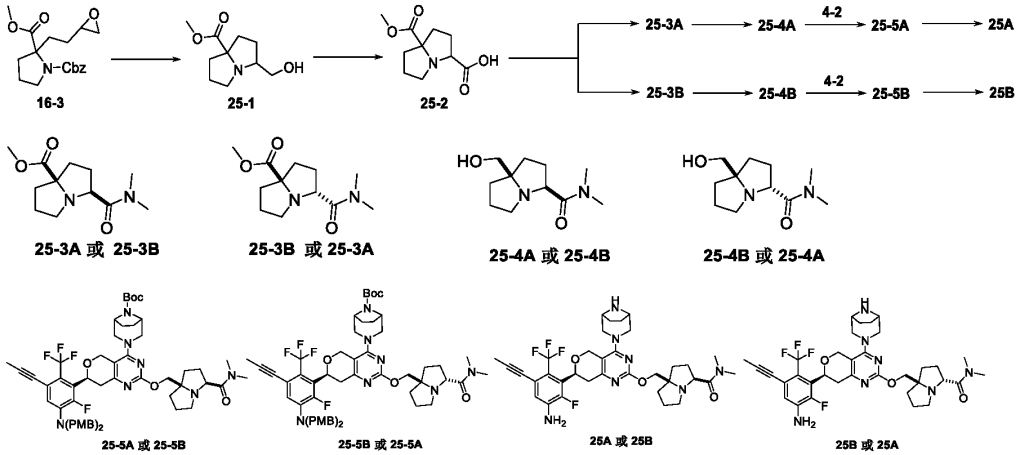
Step 7

Compound **24-6C** (10 mg, 10.00 μmol) was dissolved in methylene chloride (3 mL), and then zinc bromide (5 mg, 20.00 μmol) was added. Under nitrogen protection, the reaction was stirred at 25 °C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.1% formic acid)-acetonitrile]; acetonitrile]: 10%-40%. After lyophilization, the formate of compound **24C** was obtained. MS m/z = 700.4 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 8.39 (s, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.19 (dd, *J* = 11.2, 4.4 Hz, 1H), 4.94 (q, *J* = 6.4 Hz, 1H), 4.88 (d, *J* = 6.8 Hz, 3H), 4.72 (d, *J* = 13.8 Hz, 1H), 4.59 (q, *J* = 5.8 Hz, 2H), 4.41 (d, *J* = 6.8 Hz, 3H), 4.27 (d, *J* = 13.8 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 2H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.49 - 3.36 (m, 1H), 3.27 (d, *J* = 11.6 Hz, 2H), 3.13 (s, 1H), 2.93 (dd, *J* = 18.2, 4.4 Hz, 1H), 2.37 - 2.19 (m, 5H), 2.14 - 2.05 (m, 4H), 2.03 - 1.99 (m, 4H), 1.97 - 1.91 (m, 2H).

Compound **24-6D** (30 mg, 30.00 μmol) was dissolved in methylene chloride (3 mL), then zinc bromide (14 mg, 30.00 μmol) was added, and the reaction was stirred at 25°C for 2 hours under nitrogen protection. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.1% formic

acid)-acetonitrile]; acetonitrile]: 10%-40%. After lyophilization, the formate of compound **24D** was obtained. MS m/z=700.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.46 (s, 3H), 6.92 (d, J = 8.4 Hz, 1H), 5.19 (dd, J = 11.0, 4.0 Hz, 1H), 4.98 - 4.92 (m, 1H), 4.91 - 4.89 (m, 2H), 4.72 (d, J = 13.6 Hz, 2H), 4.60 - 4.57 (m, 2H), 4.37 - 4.23 (m, 3H), 4.21 - 4.15 (m, 1H), 4.07 (d, J = 12.6 Hz, 2H), 3.76 (d, J = 14.6 Hz, 1H), 3.63 (d, J = 13.6 Hz, 1H), 3.27 (d, J = 13.2 Hz, 3H), 3.01 - 2.96 (m, 1H), 2.95 - 2.86 (m, 1H), 2.33 - 2.13 (m, 5H), 2.13 - 2.03 (m, 4H), 2.02 (s, 3H), 1.99 - 1.85 (m, 3H).

Example 25



Step 1

Compound **16-3** (8.00 g, 24.00 mmol) was dissolved in methanol (30 mL), 10% palladium carbon (1.5 g) was added, and the reaction mixture was stirred at 25 °C for 24 hours under hydrogen gas atmosphere, the reaction mixture was filtered and the filtrate was concentrated to obtain compound 25-1. MS m/z = 200.2 $[M+H]^+$

Step 2

Periodic acid (12.30 g, 53.95 mmol) was dissolved in an acetonitrile solution (0.075% water) (50.0 mL) solution, chromium trioxide (647.40 mg, 6.47 mmol) was slowly added at 0 °C and stirred for 10 minutes. Dissolve compound **25-1** in acetonitrile (50.0 mL), slowly add it to the above mixed solution at 0 °C, add it to slowly warm to room temperature, stir for 10 hours, filter, and concentrate the filtrate under reduced pressure to obtain compound **25-2**. MS m/z = 214.2 $[M+H]^+$

Step 3

Compound **25-2** (0.90 g, 4.22 mmol) was dissolved in N,N-dimethylformamide (20 mL), benzotriazole-N,N,N',N',-tetramethyl-uronium-hexafluorophosphate (2.41 g, 6.33 mmol) and N,N-diisopropylethylamine (2.73 g, 21.10 mmol) were added, and the reaction mixture was stirred at room temperature for 30 minutes. Dimethylamine hydrochloride (1.72 g, 21.10 mmol) was added to the

above mixture and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (35 mL). The organic phase was washed with saturated brine (10 mL), dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure to obtain the crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19 mm, 5 mm; mobile phase: [water (0.1% ammonia-acetonitrile]; gradient: (acetonitrile): 10%-40% to obtain compound **25-3A** and compound **25-3B.** By LCMS analytical method (chromatographic column: Waters Xbridge C18, (50 mm × 4.6 mm × 3.5 μm); mobile phase: [A: water (0.1% ammonia water) B: acetonitrile]; gradient: B%: 0-10% and 0.2 min; 20-95% 1.8 min; 95-95% 0.7 min; 95-10% 0.1 min; 10-10% 0.7 min) compound **25-3A** Rt = 1.780 min, MS m/z = 241.2 $[M+H]^+$, and compound **25-3B** Rt = 1.833 min, MS m/z = 241.2 $[M+H]^+$]

Step 4

Compound **25-3A** (0.13 g, 540.99 μmol) was dissolved in methanol (5 mL), and sodium borohydride (61.40 mg, 1.62 mmol) and 30% sodium methanol in methanol (2.92 mg, 54.10 μmol) were added at 0 °C. The reaction mixture was stirred at 25 °C for 16 hours. After the reaction is completed, saturated ammonium chloride solution (10 ml) is added for quenching, dichloromethane (10 mL) is extracted, the organic phase is washed with saturated brine (5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 10:1) yielded compound **25-4A**. MS m/z = 213.1 $[M+H]^+$.

With reference to step 4, compound **25-3A** was replaced with compound **25-3B** as the raw material to obtain compound **25-4B**. MS m/z = 213.1 $[M+H]^+$.

Step 5

Compound **25-4A** (50.00 mg, 235.53 μmol) was dissolved in tetrahydrofuran (2 mL) and then cooled to 0 °C. NaH (16.96 mg, 706.59 μmol, 60% purity) was added and stirred for 1 hour. Compound **4-2** (50.00 mg, 235.53 μmol) was added to the above mixture and the resulting mixture was stirred and reacted at 25 °C for 1 hour. The resulting mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL). The organic phases were washed with saturated brine (2mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 10:1) yielded compound **25-5A**. MS m/z = 1012.8 $[M+H]^+$.

With reference to step 5, compound **25-4A** was replaced with compound **25-4B** as the raw material to obtain compound **25-5B**. MS m/z = 1012.8 $[M+H]^+$.

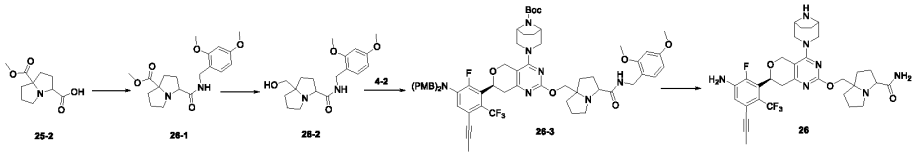
Step 6

Compound **25-5A** (0.14 g, 138.32 μmol) was dissolved in trifluoroacetic acid (2 mL) and stirred and

reacted at 25 °C for 1 hour. The reaction mixture was concentrated to remove TFA. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; [water (0.1% ammonia)-acetonitrile]; gradient: (acetonitrile): 30%-70% mobile phase: A water (0.1% ammonia water) and B (acetonitrile); gradient: B% = 30% - 70%, and compound **25A** was obtained after lyophilization. MS m/z = 672.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.13 - 5.09 (m, 1H), 4.78 - 4.67 (m, 2H), 4.54 (d, *J* = 8.0 Hz, 1H), 4.35 - 4.28 (m, 1H), 4.26 - 4.23 (m, 1H), 4.13 - 4.09 (m, 1H), 3.91 - 3.88 (m, 1H), 3.27 - 3.19 (m, 2H), 3.16 - 3.10 (m, 4H), 2.94 - 2.88 (m, 4H), 2.79 - 2.66 (m, 4H), 2.22 - 2.15 (m, 2H), 2.11 - 1.89 (m, 11H), 1.78 - 1.75 (m, 1H), 1.72 - 1.66 (m, 1H)。

Compound **25-5B** (60.00 mg, 59.28 μmol) was dissolved in trifluoroacetic acid (1 mL) and stirred and reacted at 25 °C for 1 hour. The reaction mixture was concentrated to remove TFA. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19mm, 5mm; [water (0.1% ammonia)-acetonitrile]; gradient: (acetonitrile): 30%-70% mobile phase: A water (0.1% ammonia water) and B (acetonitrile); gradient: B% = 30% - 70%, and compound **25B** was obtained after lyophilization. MS m/z = 672.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.13 - 5.10 (m, 1H), 4.78 - 4.67 (m, 2H), 4.52 - 4.47 (m, 1H), 4.32 - 4.28 (m, 1H), 4.26 - 4.21 (m, 1H), 4.15 - 4.10 (m, 1H), 3.91 - 3.87 (m, 1H), 3.27 - 3.22 (m, 2H), 3.15 - 3.13 (m, 3H), 2.93 - 2.92 (m, 3H), 2.80 - 2.72 (m, 4H), 2.67 - 2.66 (m, 1H), 2.54 - 2.50 (m, 1H), 2.18 - 2.04 (m, 3H), 2.02 - 1.89 (m, 7H), 1.83 - 1.74 (m, 4H), 1.62 - 1.55 (m, 1H)。

Example 26



Step 1

Compound **25-2** (1.00 g, 4.69 mmol) was dissolved in N, N-dimethylformamide (20 mL), followed by addition of N, N-diisopropylethylamine (2.12 g, 16.41 mmol), N,N,N′,N′-tetramethyl-O-(7-azabenzotriazole-1-yl) hexafluorourea phosphate (2.67 g, 7.03 mmol), 2, 4-dimethoxybenzoamine 1.02 g, 6.10 mmol) and reaction at 25 °C for 2 hours. The reaction solution was added with water (50 mL), extracted with ethyl acetate (40 mL * 3), concentrated under reduced pressure, and column chromatography separated (petroleum ether: ethyl acetate = 2:3) to obtain compound **26-1**. MS m/z = 363.5 $[M+H]^+$.

Step 2

Compound **26-1** (50.00 mg, 137.96 μmol) was dissolved in ethanol (1 mL of tetrahydrofuran (0.6

mL), lithium chloride (11.70 mg, 275.92 μmol), sodium borohydride (10.44 mg, 275.92 μmol), and reacted at 50 °C for 3 hours. Cool to room temperature, add DCM (20 mL), saturated saline (3 mL* 3) wash, dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure to obtain compound **26-2**. MS m/z = 335.3 $[M+H]^+$.

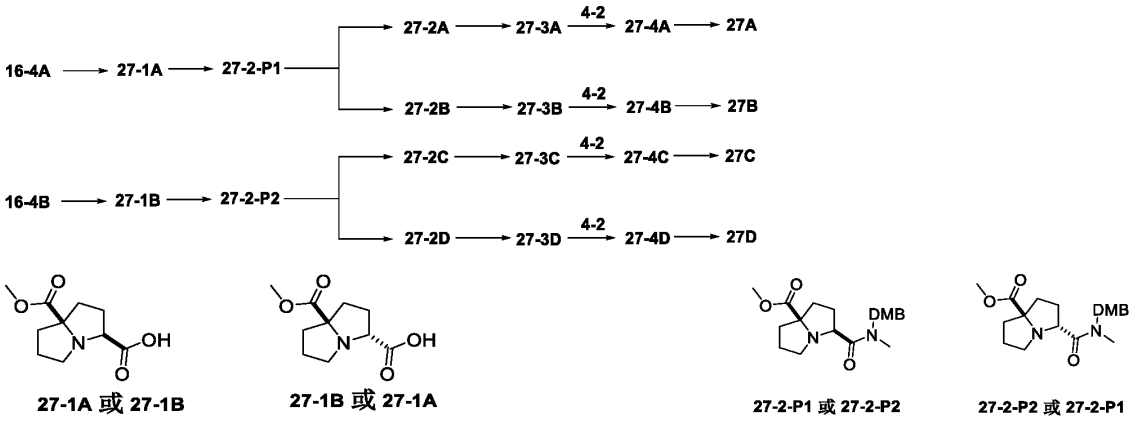
Step 3

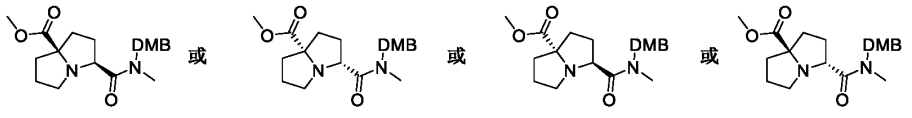
Compound **26-2** (30.00 mg, 89.71 μmol) was dissolved in tetrahydrofuran (3 mL), sodium tert-butanol (43.11 mg, 44.85 μmol) was added, stirred for 0.5 hour, and compound **4-2**77.51 mg, 89.71 μmol) was added finally, and reacted at 25 °C for 1 hour. Add water (3 mL) to quench the reaction, extract with ethyl acetate (20 mL), concentrate under reduced pressure, and separate by column chromatography (petroleum ether: ethyl acetate = 1:4) to obtain compound **26-3**. MS m/z = 1134.6 $[M+H]^+$.

Step 4

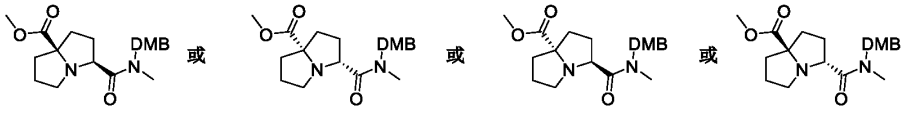
Compound **26-3** (50.00 mg, 44.08 μmol) was dissolved in trifluoroacetic acid (1 mL) and reacted at 70 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters SunFire, 250*19 mm, 5 μm; mobile phase: [water (0.1% formic acid) - acetonitrile]; gradient: (acetonitrile): 40%-75%. After lyophilization, the formate of compound **26** was obtained. MS m/z= 644.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.38 (brs, 1H), 6.91 (d, J = 8.5 Hz, 1H), 5.20 - 5.12 (m, 1H), 4.82 - 4.66 (m, 4H), 4.47 (d, J = 6.4 Hz, 1H), 4.27 (q, J = 10.8 Hz, 2H), 3.58 (d, J = 12.5 Hz, 1H), 3.52 - 3.41 (m, 1H), 3.26 - 3.15 (m, 4H), 2.91 - 2.77 (m, 2H), 2.38 - 2.28 (m, 2H), 2.20 - 2.09 (m, 2H), 2.07 - 1.93 (m, 9H), 1.86 - 1.71 (m, 2H).

Example 27

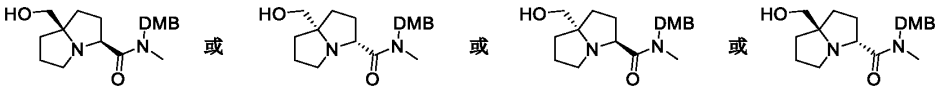




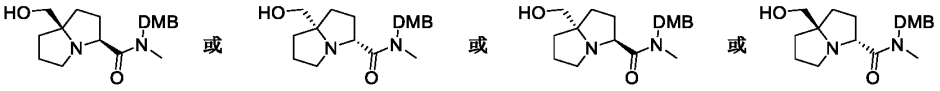
27-2A 或 27-2B



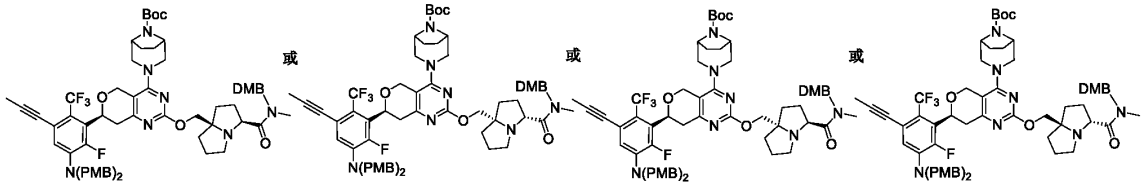
27-2C 或 27-2D



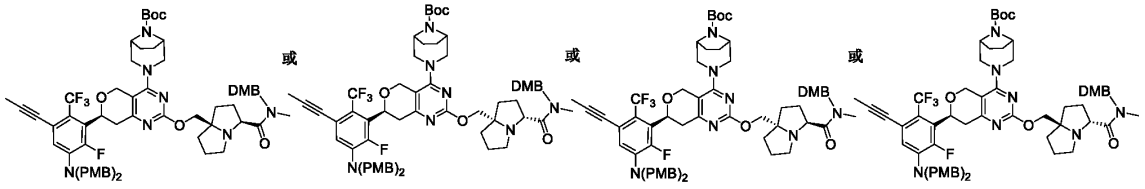
27-3A 或 27-3B



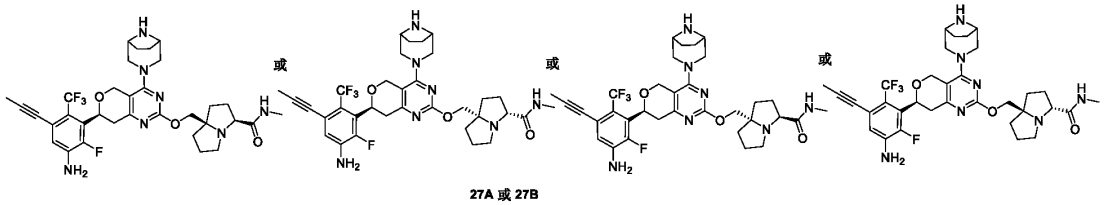
27-3C 或 27-3D



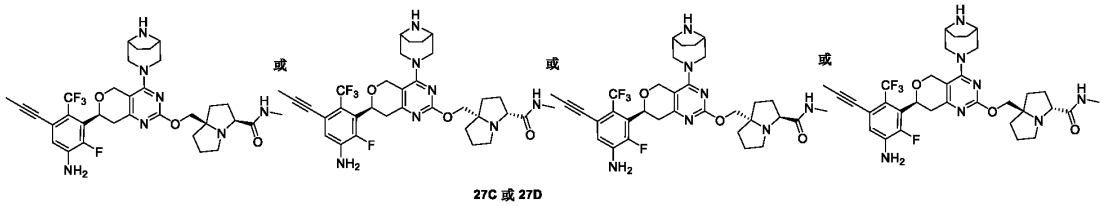
27-4A 或 27-4B



27-4C 或 27-4D



27A 或 27B



27C 或 27D

Step 1

Dissolve periodine acid (1.71 g, 7.54 mmol) in 15 mL of mixed solvent (acetonitrile: Water =

100:0.75), chromium trioxide (89.54 mg, 0.90 mmol) was added at 0 °C, and stirred for 15 minutes. Compound **16-4A** (0.60 g 3.02 mmol) was dissolved in acetonitrile (15 mL), slowly added to the above mixed solution at 0 °C. After addition, the mixture was slowly heated to room temperature, stirred for 16 hours, the reaction solution was filtered, and the filtrate was concentrated under reduced pressure to obtain compound **27-1A**, MS m/z = 214.0 $[M+H]^+$.

With reference to step 1, compound **16-4A** was replaced with compound **16-4B** to obtain compound **27-1B**. MS m/z =214.0 $[M+H]^+$.

Step 2

Compound **27-1A** (0.20 g, 0.94 mmol) was dissolved in N, N-dimethylformamide (5 mL), followed by addition of 2,4-dimethoxy-N-methylaniline (254.92 mg 1.41 mmol), N, N-diisopropylethylamine (605.63 mg 4.69 mmol), 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (606.57 mg 1.60 mml) for 1 h at room temperature. Add 25 mL of water to the reaction solution, extract with ethyl acetate (15 mL * 3), combine the organic phases, wash successively with water (10 mL * 2) and saturated esophagus saline (10 mL), dry with anhydrous sodium sulfate, filter, and concentrate. Column chromatography (dichloromethane: methanol = 20:1) yielded compound **27-2-P1**, MS m/z = 377.1 $[M+H]^+$.

Compound **27-2-P1** was prepared for SFC separation (chromatographic column: DAICEL CHIRALPAK®AS-10, 25*250 mm 10 μm; mobile phase: A: supercritical carbon dioxide, B: [0.05% ammonia methanol-ethanol]; B%: 80%-20% to obtain compound **27-2A** and compound **27-2B**. After analysis SFC (column: DAICEL CHIRALPAK®AS-10 (4.6 mmI.D*150 mmL, 5 μm) mobile phase: [A: supercritical carbon dioxide, B: ethanol (0.05% diethylamine)]; gradient: B%: 5%-40%, 4 min), compound **27-2A** Rt = 2.824 min, ee value 99.05%, MS m/z = 377.1 $[M+H]^+$; compound **27-2B** Rt = 3.327 min, ee 99.10%, MS m/z = 377.1 $[M+H]^+$.

With reference to step 2, compound **27-1A** was replaced with compound **27-1B** to obtain compound **27-2-P2**. MS m/z = 377.1 $[M+H]^+$.

Compound **27-2-P2** was prepared for SFC separation (chromatographic column: DAICEL CHIRALPAK®AS-10, 25*250 mm 10 μm; mobile phase: A: supercritical carbon dioxide, B: [0.05% ammonia-methanol]; B%: 80%-20% to obtain compound **27-2C** and compound **27-2D**. After analysis, SFC (column: DAICEL CHIRALPAK®AS-10 (4.6 mmI.D*150 mmL, 5 μm) was analyzed; mobile phase: [A: supercritical carbon dioxide, B: ethanol (0.05% diethylamine)]; gradient: B%: 5%-40%, 4 min), compound **27-2C** Rt = 2.891 min, ee value 95.80%, MS m/z = 377.1 $[M+H]^+$; compound **27-2D** Rt = 3.327 min, ee value 96.34%, MS m/z = 377.1 $[M+H]^+$.

Step 3

Compound **27-2A** (80.00 mg, 0.21 mmol) was dissolved in methanol (5 mL), sodium methanol

solution (7.66 mg, 0.04 mmol, 30% purity) and sodium borohydride (24.2 mg, 0.63 mmol) were added and stirred at 25 °C for 16 hours. 3 mL of saturated aqueous ammonium chloride was added for quenching, extracted with dichloromethane (5 mL*3), combined with the extracted organic phase, washed with 5 mL of saturated salt solution, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and column chromatography separated (dichloromethane: ethyl acetate = 20:1) to obtain compound **27-3A**. MS m/z =349.1 $[M+H]^+$.

With reference to step 3, compound **27-2A** was replaced with compound **27-2B** as the raw material to obtain compound **27-3B**. MS m/z =349.1 $[M+H]^+$.

With reference to step 3, compound **27-2A** was replaced with compound **27-2C** as the raw material to obtain compound **27-3C**. MS m/z =349.1 $[M+H]^+$.

With reference to step 3, compound **27-2A** was replaced with compound **27-2D** as the raw material to obtain compound **27-3D**. MS m/z =349.1 $[M+H]^+$.

Step 4

Compound **27-3A** (60.00 mg, 0.17 mmol) was dissolved in tetrahydrofuran (5 mL), sodium hydrogen (34.48 mg, 0.85 mmol, 60% purity) was added at 0 °C, and the reaction was stirred for 0.5 hours. The solution of compound **4-2** (164.56 mg, 0.19 mmol) in tetrahydrofuran (1 mL) was then added to the above system and heated to 25 °C for continued stirring and reacting for 1 hour. The reaction was quenched by adding 6 mL of saturated aqueous ammonium chloride solution, extracted with ethyl acetate (5 mL*2), combined with the extracted organic phase, washed with 5 mL of saturated brine, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and column chromatography separated (dichloromethane: methanol = 20:1) to obtain compound **27-4A**. MS m/z =1148.5 $[M+H]^+$.

With reference to step 4, compound **27-3A** was replaced with compound **27-3B** as the raw material to obtain compound **27-4B**. MS m/z =1148.5 $[M+H]^+$.

With reference to step 4, compound **27-3A** was replaced with compound **27-3C** as the raw material to obtain compound **27-4C**. MS m/z =1148.5 $[M+H]^+$.

With reference to step 4, compound **27-3A** was replaced with compound **27-3D** as the raw material to obtain compound **27-4D**. MS m/z =1148.5 $[M+H]^+$.

Step 5

Compound **27-4A** (0.10 g, 87.15 μmol) was dissolved in trifluoroacetic acid (3 mL), and the reaction was stirred and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19 mm, 5 μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; acetonitrile): 50%-70%), the compound **27A** was

obtained after lyophilization. MS m/z= 658.6[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.10 (m, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 4.16 - 4.07 (m, 2H), 3.57 - 3.48 (m, 3H), 3.45 - 3.38 (m, 1H), 3.29 - 3.17 (m, 2H), 3.10 - 3.01 (m, 2H), 2.89 - 2.81 (m, 1H), 2.73 (s, 3H), 2.67 - 2.60 (m, 1H), 2.31 - 2.23 (m, 1H), 2.15 - 2.08 (m, 1H), 2.04 - 1.96 (m, 4H), 1.95 - 1.87 (m, 4H), 1.86 - 1.79 (m, 2H), 1.76 - 1.65 (m, 3H).

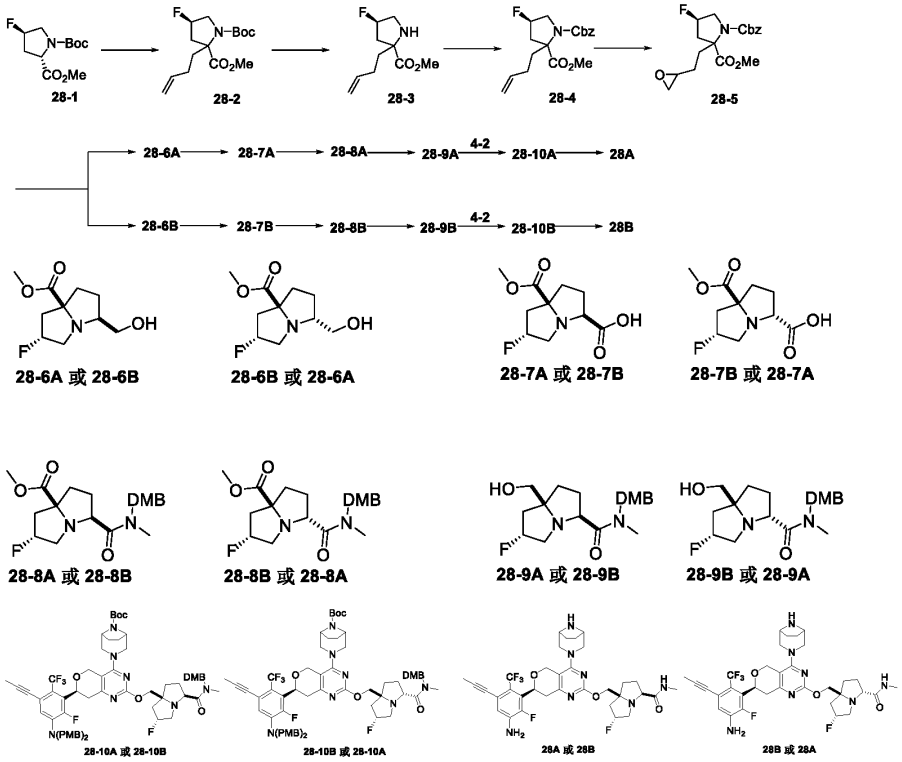
Compound **27-4B** (80.00 mg, 69.71 μmol) was dissolved in trifluoroacetic acid (3 mL), and the reaction was stirred and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19 mm, 5 μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; acetonitrile): 50%-70%), and compound **27B** was obtained after lyophilization. MS m/z= 658.5[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 9.0 Hz, 1H), 4.16 - 4.06 (m, 2H), 3.57 - 3.48 (m, 3H), 3.44 - 3.38 (m, 1H), 3.30 - 3.15 (m, 2H), 3.10 - 3.01 (m, 2H), 2.89 - 2.80 (m, 1H), 2.73 (s, 3H), 2.68 - 2.60 (m, 1H), 2.31 - 2.21 (m, 1H), 2.19 - 2.09 (m, 1H), 2.01 - 1.96 (m, 4H), 1.94 - 1.78 (m, 6H), 1.77 - 1.64 (m, 3H).

Compound **27-4C** (90.00 mg, 78.36 μmol) was dissolved in trifluoroacetic acid (3 mL), and the reaction was stirred and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. Preparation of crude product for high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19 mm, 5μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; acetonitrile): 50%-70%). After lyophilization, compound **27C** was obtained. MS m/z= 658.3[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.10 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.10 (m, 2H), 4.10 - 4.05 (m, 1H), 3.76 - 3.71 (m, 1H), 3.57 - 3.48 (m, 3H), 3.45 - 3.38 (m, 1H), 3.26 - 3.16 (m, 1H), 3.04 (d, *J* = 12.7 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.75 (s, 3H), 2.75 - 2.68 (m, 1H), 2.14 - 2.05 (m, 2H), 2.04 - 1.97 (m, 5H), 1.96 - 1.80 (m, 6H), 1.76 - 1.64 (m, 2H).

Compound **27-4D** (95.00 mg, 82.28 μmol) was dissolved in trifluoroacetic acid (3 mL), and the reaction was stirred and reacted at 25 °C for 1 hour. The reaction solution was concentrated under reduced pressure to obtain crude product. The crude product was prepared by high performance liquid chromatography separation (chromatographic column: Waters Xbridge, 250*19 mm, 5 μm; mobile phase: [water (0.1% ammonia water)-acetonitrile]; acetonitrile): 50%-70%). After lyophilization, compound **27D** was obtained. MS m/z= 658.4[M+H]$^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.07 - 4.01 (m, 1H), 3.76 - 3.71 (m, 1H), 3.56 - 3.48 (m, 3H), 3.45 - 3.38 (m, 1H), 3.26 - 3.17 (m, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.75 (s, 3H), 2.75 - 2.69 (m, 1H), 2.15 -

2.06 (m, 2H), 2.05 - 1.97 (m, 5H), 1.96 - 1.80 (m, 6H), 1.76 - 1.65 (m, 2H)。

Example 28



Step 1

Weigh compound **28-1** (1 g, 4.04 mmol), add anhydrous tetrahydrofuran (10 mL) under nitrogen protection, carry out dry ice bath to -76 °C, slowly add lithium bis(trimethylsilyl)amide (12.12 mL, 12.12 mmol, 1M), stir at -76 °C for 40 minutes, add 4-bromobutene (654.48 mg, 4.84 mmol) in anhydrous tetrahydrofuran solution (5 mL), continue stirring for 60 minutes. The reaction was quenched by adding saturated aqueous ammonium chloride solution (10 mL), extracted with ethyl acetate (15 mL * 3), combined with the extracted organic phase, washed with saturated brine (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (ethyl acetate: petroleum ether = 1:7) yielded compound **28-2**. MS m/z = 302.2 $[M+H]^+$

Step 2

Weigh compound **28-2** (500 mg, 1.66 mmol), add dichloromethane (3 mL), hydrochloric acid/1,4-dioxane solution (3 mL), and react at room temperature for 30 minutes. The reaction solution was directly concentrated to obtain the hydrochloride of compound **28-3**, MS m/z = 202.1 $[M+H]^+$

Step 3

Weigh compound **28-3** (500 mg, hydrochloride), add anhydrous tetrahydrofuran (10 mL), add sodium

hydride (148.80 mg, 3.72 mmol, 60% purity) under ice bath at 0 °C, stir at 0 °C for 1 hour, add benzyl chloroformate (634.59 mg, 3.72 mmol) in batches, and stir at 40 °C for 16 hours. The reaction was quenched with water (15 mL), extracted with ethyl acetate (20 mL * 3), combined with the extracted organic phase, washed with saturated brine (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Column chromatography separation (ethyl acetate : Petroleum ether = 1:8) obtained compound **28-4**, MS m/z = 336.2 $[M+H]^+$.

Step 4

Weigh compound **28-4** (300 mg, 0.89 mmol), add methylene chloride (5 mL), add m-chloroperoxybenzoic acid (307.17 mg, 1.78 mmol), and stir and reacted at room temperature for 2 hours. Add saturated sodium sulphite aqueous solution (1 mL) to the reaction solution, stir for 5 minutes, add water (10 mL), add methylene chloride (15 mL * 3) for extraction, combine the extracted organic phases, wash with saturated edible brine (20 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Column chromatography separation (ethyl acetate Petroleum ether = 1:6) to obtain compound **28-5**, MS m/z = 352.2 $[M+H]^+$.

Step 5

Weigh compound **28-5** (1 g, 2.85 mmol), add anhydrous methanol (10 mL), add 10% palladium carbon (100 mg), and replace with hydrogen gas three times. Stir at room temperature for 1 hour. The reaction solution was directly filtered, the cake was washed with methanol (10 mL), and the filtrate was concentrated under reduced pressure. Column chromatography separation (dichloromethane: methanol = 50:1) yielded compound **28-6A** (unfolding agent: DCM/MeOH = 15:1, Rf = 0.5), MS m/z = 218.1 $[M+H]^+$, and compound **28-6B** (unfolding agent: DCM/MeOH = 15:1, Rf = 0.3 MS m/z = 218.1 $[M+H]^+$

Compound **28-6A**: ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 5.39 - 5.21 (m, 1 H), 4.37 (d, *J* = 8.0 Hz, 1H), 3.58 (s, 3H), 3.39 - 3.35 (m, 1H), 3.29 - 3.21 (m, 2H), 2.99 - 2.86 (m, 1H), 2.82 - 2.77 (m, 1H), 2.61 - 2.52 (m, 1H), 2.09 - 1.91 (m, 3H), 1.84 - 1.78 (m, 1H), 1.68 - 1.60 (m, 1H).

Compound **28-6B**: ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 5.27 - 5.10 (m, 1 H), 4.64 (d, *J* = 8.0 Hz, 1H), 3.59 (s, 3H), 3.58 - 3.54 (m, 1H), 3.51 - 3.46 (m, 1H), 3.25 - 3.18 (m, 1H), 3.09 - 2.95 (m, 2H), 2.69 - 2.60 (m, 1H), 2.02 - 1.70 (m, 4H), 1.59 - 1.48 (m, 1H).

Step 6

Compound **28-6A** (200.00 mg, 920.65 mmol) was weighed, acetonitrile (2 mL) and water (0.014 mL) were added, and the temperature was reduced to 0 °C. Periodic acid (662.87 mg, 2.30 mmol) was added, chromium trioxide (27.62 mg, 1.84 mmol) was added, and the reaction was performed at room temperature for 4 hours. The reaction solution was filtered, the filter cake was washed with 10 mL of dichloromethane, and the filtrate was concentrated to obtain compound **28-7A**, MS m/z = 232.1

$[M+H]^+$.

With reference to step 6, compound **28-6A** was replaced with compound **28-6B** as the raw material to obtain compound **28-7B**. MS m/z = 232.1 $[M+H]^+$.

Step 7

Compound **28-7A** (120 mg, 518.99 μmol) was dissolved in N,N-dimethylformamide (3 mL), N-methyl-3,4-dimethylbenzylamine (92.94 mg, 622.79 μmol), 2-(7-azabenzotriazazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (394.67 mg, 1.04 mmol), N,N-diisopropylethylamine (201.22 mg, 1.56 mmol) was added and reacted at 25°C for 4 hours. Extracted with ethyl acetate (20 mL*2), combined with the extracted organic phase, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. Column chromatography separation (petroleum ether: Ethyl acetate = 10:1-1:1) to obtain compound **28-8A**. MS m/z = 395.2 $[M+H]^+$.

With reference to step 7, compound **28-7A** was replaced with compound **28-7B** as the raw material to obtain compound **28-8B**. MS m/z = 395.2 $[M+H]^+$.

Step 8

Compound **28-8A** (20.00 mg, 55.18 μmol) was dissolved in methanol (0.5 mL), sodium borohydride (4.18 mg, 110.36 μmol) was added, and sodium methanol (29.81 μg, 0.55 μmol) was added. React at 25 °C for 4 hours. Extract with ethyl acetate (20 mL*2), combine the extracted organic phases, wash with saturated brine (20 mL), dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure to obtain compound **28-9A**. MS m/z = 367.3 $[M+H]^+$.

With reference to step 8, compound **28-8A** was replaced with compound **28-8B** as the raw material to obtain compound **28-9B**. MS m/z = 367.3 $[M+H]^+$.

Step 9

Compound **28-9A** (20 mg, 54.58 μmol) was dissolved in anhydrous tetrahydrofuran (0.5 mL), cooled to 0 °C, sodium hydrogen (2.62 mg, 109.16 μmol, 60% purity) was added under nitrogen protection, and reacted at room temperature for 1 hour. The reaction was quenched by adding 5 mL of saturated ammonium chloride solution, extracted with ethyl acetate (10 mL*2), combined with the extracted organic phase, washed with saturated brine (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Preparation thin layer chromatography purification (dichloromethane: methanol = 20:1) was prepared to obtain compound **28-10A**. MS m/z = 1166.5 $[M+H]^+$.

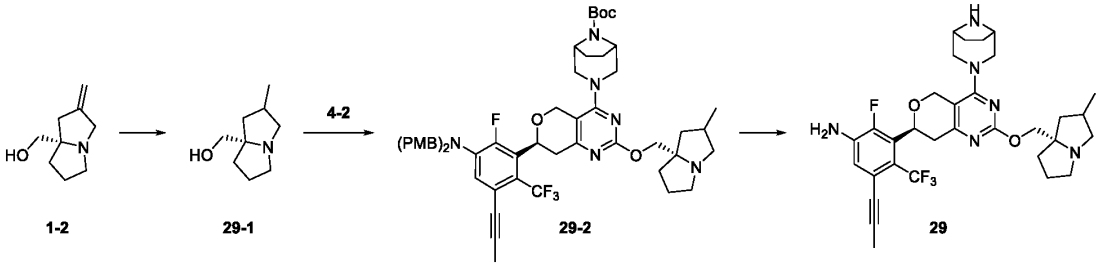
With reference to step 9, compound **28-9A** was replaced with compound **28-9B** as the raw material to obtain compound **28-10B**. MS m/z = 1166.5 $[M+H]^+$.

Step 10

Compound **28-10A** (20 mg, 17.63 μmol) was added to dichloromethane (1 mL) and trifluoroacetic acid (0.1 mL), and the solution was stirred and reacted at 20°C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Xtimate C18 150 * 40 mm * 5 μm; mobile phase: [water (0.05% formic acid)-acetonitrile]; gradient: (acetonitrile): 10%-40 %); after lyophilization, the formate of compound **28A** was obtained. MS m/z = 676.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 (brs, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.49 - 5.27 (m, 1H), 5.17 (dd, *J* = 11.6, 4.5 Hz, 1H), 4.82 - 4.79 (m, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.30 - 4.19 (m, 2H), 3.91 (s, 2H), 3.71 - 3.64 (m, 1H), 3.59 - 3.42 (m, 2H), 3.29 - 3.12 (m, 3H), 3.04 - 2.85 (m, 2H), 2.73 (s, 3H), 2.44 - 2.29 (m, 2H), 2.23 - 2.15 (m, 2H), 2.07 - 1.98 (m, 6H), 1.97 - 1.75 (m, 3H).

Compound **28-10B** (20 mg, 17.63 μmol) was added to dichloromethane (1 mL) and trifluoroacetic acid (0.1 mL), and the solution was stirred and reacted at 20°C for 2 hours. The reaction solution was concentrated under reduced pressure to obtain crude product. Crude product was prepared for high performance liquid chromatography separation (chromatographic column: Xtimate C18 150*40mm*5μm; mobile phase: [water (0.05% hydrochloric acid)-acetonitrile]; gradient: (acetonitrile: 10%-40%. After lyophilization, the hydrochloride of compound 28B is obtained. MS m/z= 676.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.42 - 5.25 (m, 1H), 5.18 - 5.11 (m, 1H), 4.79 (d, *J* = 13.5 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 8.0 Hz, 1H), 4.20 - 4.11 (m, 2H), 3.75 (t, *J* = 5.6 Hz, 1H), 3.52 (d, *J* = 12.0 Hz, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.12 (m, 2H), 3.10 - 2.99 (m, 2H), 2.88 - 2.80 (m, 1H), 2.73 (s, 3H), 2.45 - 2.35 (m, 1H), 2.24 - 2.07 (m, 2H), 2.06 - 1.96 (m, 7H), 1.87 - 1.77 (m, 2H), 1.68 (t, *J* = 8.9 Hz, 1H).

Example 29



Step 1

To a stirred solution of compound **1-2** (50.00 mg, 326.33 μmol) in MeOH (2 mL) was added Pd/C (16.64 mg, 10% purity) and the mixture was stirred at 20 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **29-1**. MS m/z =156.15 $[M+H]^+$.

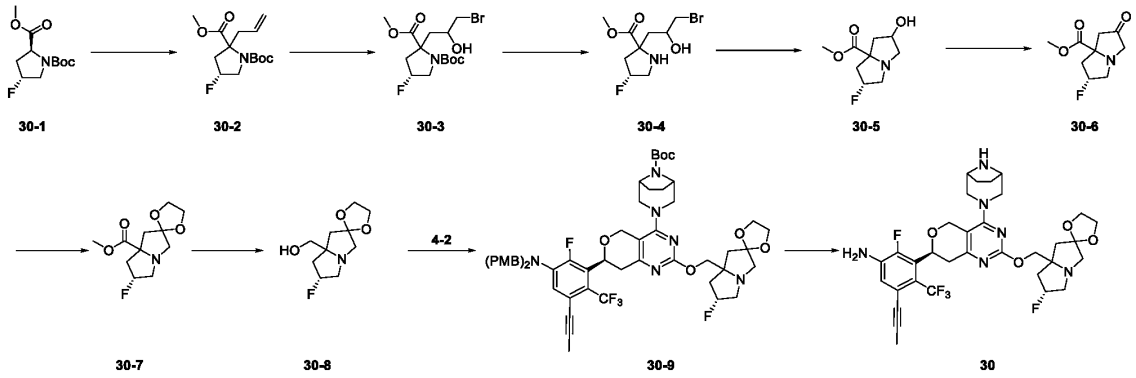
Step 2

To a stirred solution of compound **29-1** (52.00 mg, 334.97 μmol) in dry THF (4 mL) was added potassium tert-butoxide (257.54 mg, 2.68 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 hour. Then compound **4-2** (347.28 mg, 401.97 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (5 mL), extracted wtih EtOAc (2 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **29-2**. MS m/z = 955.2 $[M+H]^+$.

Step 3

The mixture of compound **29-2** (0.11 g, 115.17 μmol) in TFA (1 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 45%-75%) to afford compound **29** as a FA salt. MS m/z = 615.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.53 (s, 0.71H), 6.93 (d, *J* = 12.0 Hz, 1H), 5.18 - 5.15 (m, 1H), 4.80 - 4.73 (m, 3H), 4.62 - 4.60 (m, 1H), 4.49 - 4.43 (m, 3H), 3.78 - 3.72 (m, 1H), 3.52 - 3.36 (m, 2H), 3.30 - 3.17 (m, 2H), 3.02 - 2.99 (m, 1H), 2.91- 2.87 (m, 2H), 2.83 - 2.75 (m, 2H), 2.62 - 2.42 (m, 1H), 2.35 - 2.26 (m, 1H), 2.21 - 2.18 (m, 3H), 2.10 - 2.06 (m, 2H), 2.04 (m, 5H), 1.90 - 1.70 (m, 1H), 1.20 - 1.15 (m, 3H).

Example 30



Step 1

To a stirred solution of compound **30-1** (10 g, 40.44 mmol) in dry THF (100 mL) was added lithium bis(trimethylsilyl)amide (1 M, 52.58 mmol, 52.58 mL) at -78 °C and the mixture was stirred at -78 °C for 0.5 hours. Then allyl bromide (5.87 g, 48.53 mmol) was added at -78 °C, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution (100 mL), extracted wtih EtOAc (3 × 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound

30-2. MS m/z = 288.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **30-2** (200mg, 696.07 μmol) in THF (1 mL) and water (1 mL) was added N-bromosuccinimide (123.89 mg, 696.07 μmol) portionwise. The reaction was quenched with saturated $NaHCO_3$ solution (3 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 4:1) to afford compound **30-3**. MS m/z = 384.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **30-3** (400 mg, 1.04 mmol) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The reaction was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford compound **30-4**. MS m/z = 284.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **30-4** (295.78 mg, 1.04 mmol) in acetonitrile (4 mL) was added K_2CO_3 (719.38 mg, 5.21 mmol). The reaction was stirred at 80 °C for 3 hours. The reaction was cooled down to room temperature and filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **30-5**. MS m/z = 204.3 $[M+H]^+$.

Step 5

To a stirred solution of compound **30-5** (500 mg, 2.46 mmol) in DCM (4 mL) was added Dess-Martin periodinane (3.13 g, 7.38 mmol) at 0 °C. The reaction was stirred at 25 °C for 2 hours. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **30-6**. MS m/z = 202.1 $[M+H]^+$.

Step 6

To a stirred solution of compound **30-6** (240 mg, 1.19 mmol) in toluene (5 mL) was added ethylene glycol (0.37 g, 5.96 mmol) and p-toluenesulfonic acid monohydrate (22.69 mg, 0.12 mmol) at 25 °C. The reaction was stirred at 90 °C for 16 hours. The reaction was cooled down to room temperature and quenched with saturated $NaHCO_3$ solution (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **30-7**. MS m/z = 246.1 $[M+H]^+$.

Step 7

To a stirred solution of compound **30-7** (100 mg, 0.41 mmol) in dry THF (5 mL) was added

lithium aluminum hydride (15.48 mg, 0.41 mmol) at 0 °C. The reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (0.02 mL), 15% NaOH solution (0.02 mL) and water (0.06 mL). The resulting mixture was stirred at 25 °C for 0.5 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **30-8**. MS m/z = 218.2 $[M+H]^+$.

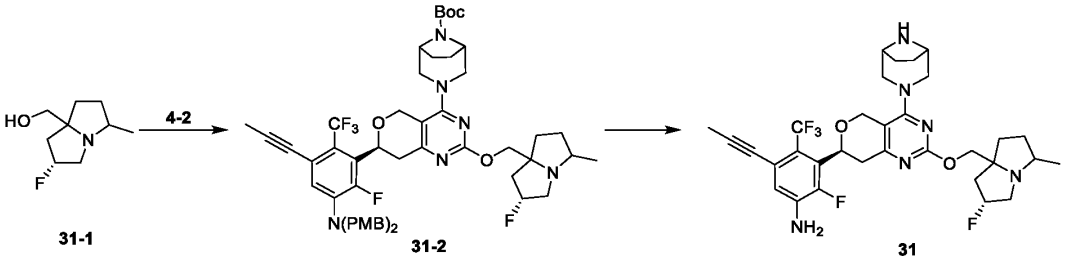
Step 8

To a stirred solution of compound **30-8** (60 mg, 0.28 mmol) in dry THF (1 mL) was added sodium hydride (55.23 mg, 1.38 mmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (264.70 mg,0.30 mmol) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **30-9**. MS m/z = 1017.7 $[M+H]^+$.

Step 9

The mixture of compound **30-9** (0.10 g, 0.098 mmol) in TFA (2.5 mL) and DCM (7.5 mL) was stirred at 25 °C for 4 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-70%) to afford compound **30**. MS m/z = 677.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.96 (d, J = 8.0 Hz, 1H), 5.42 - 5.28 (m, 1H), 5.20 - 5.17 (m, 1H), 4.85 - 4.47 (m, 2H), 4.62 - 4.60 (m, 1H), 4.46 - 4.41 (m, 1H), 4.35 - 4.27 (m, 2H), 4.03 - 3.92 (m, 4H), 3.55 - 3.38 (m, 3H), 3.31 - 3.18 (m, 3H), 3.08 - 2.99 (m, 1H), 2.92 - 2.84 (m, 3H), 2.59 - 2.49 (M, 1H), 2.43 - 2.35 (m, 1H), 2.31 - 2.16 (m, 2H), 2.12 - 2.01 (m, 7H).

Example 31



Step 1

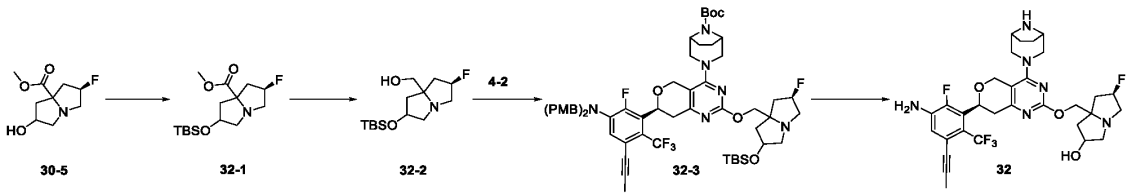
To a stirred solution of compound **31-1** (20 mg, 57.87 μmol) in dry THF (3 mL) was added sodium hydride (4.63 mg, 115.75 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (50 mg, 57.87 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc

(3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **31-2**. MS m/z = 973.7 $[M+H]^+$.

Step 2

The mixture of compound **31-2** (40 mg, 41.11 μmol) in TFA (4 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-70%) to afford compound **31**. MS m/z = 633.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.47 - 5.45 (m, 0.5H), 5.34 - 5.31 (m, 0.5H), 5.17 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 4.80 (s, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.57 (s, 1H), 4.25 (d, *J* = 12.0 Hz, 2H), 4.12 (d, *J* = 12.0 Hz, 1H), 3.89 - 3.85 (m, 2H), 3.69-3.62 (m, 1H), 3.58 - 3.53 (m, 1H), 3.47 - 3.37 (m, 1H), 3.21 - 3.15 (m, 1H), 3.07 - 2.83 (m, 3H), 2.47 (dd, *J* = 20.0 Hz, 16.0 Hz, 1H), 2.25 - 2.15 (m, 2H), 2.08 - 1.93 (m, 7H), 1.88 - 1.70 (m, 3H), 1.16 (d, *J* = 8.0 Hz, 3H).

Example 32



Step 1

To a stirred solution of compound **30-5** (110.00 mg, 0.54 mmol) in DCM (5 mL) was added tert-butyldimethylsilyl chloride (162.76 mg, 1.08 mmol) and imidazole (110.16 mg, 1.62 mmol) at 25 °C. The reaction was stirred at 25 °C for 16 hours. The reaction was quenched with water (10 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **32-1**. MS m/z = 318.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **32-1** (85 mg, 0.27 mmol) in dry THF (3 mL) was added lithium aluminum hydride (0.22 mL, 0.54 mmol, 2.5 M in THF) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 15 minutes. The reaction was quenched with water (0.2 mL), 15% NaOH solution (0.2 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 10 minutes. The reaction was filtered, the filter was washed with THF (5 mL), the filtrate was concentrated under

reduced pressure to afford compound **32-2**. MS m/z = 290.2 $[M+H]^+$.

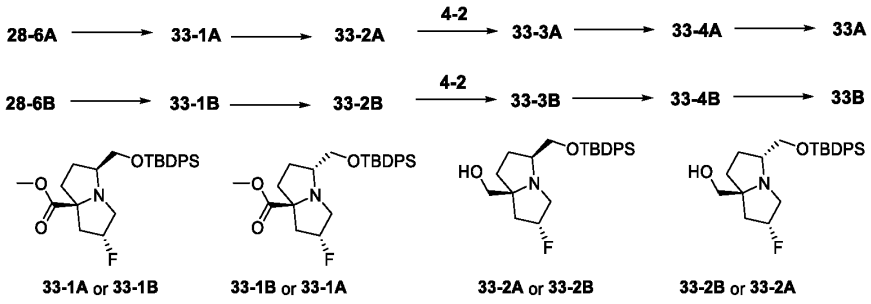
Step 3

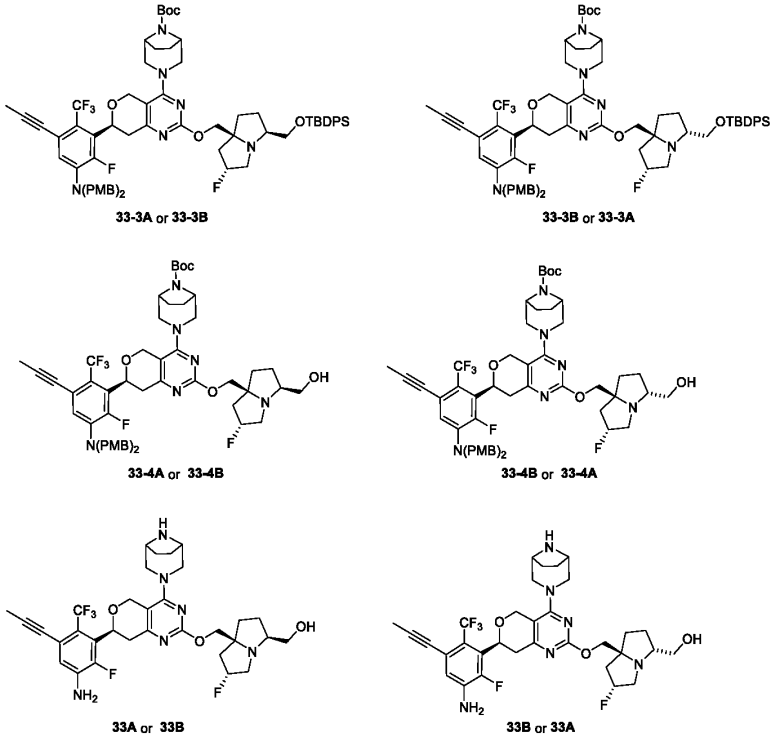
To a stirred solution of compound **32-2** (64 mg, 0.22 mmol) in dry THF (5 mL) was added sodium hydride (15.91 mg, 0.66 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 30 minutes. Then compound **4-2** (195.41 mg, 0.22 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **32-3**. MS m/z = 1089.5 $[M+H]^+$.

Step 4

The mixture of compound **32-3** (50 mg, 0.05 mmol) in TFA (1 mL) and DCM (2 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%HCl); Gradient: (ACN): 10%-40%) to afford compound **32** as HCl salt. MS m/z = 635.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, J = 8.0 Hz, 1H), 5.57 (d, J = 48.0 Hz, 1H), 5.23 (d, J = 12.0 Hz, 1H), 5.0 - 5.04 (m, 1H), 4.99 - 4.90 (m, 4H), 4.76 (t, J = 4.0 Hz, 1H), 4.23 (d, J = 28.0 Hz, 2H), 4.12 - 3.95 (m, 3H), 3.73 - 3.51 (m, 4H), 3.35 - 3.43 (m, 1H), 3.07 - 3.03 (m, 1H), 2.85 - 2.76 (m, 1H), 2.67 - 2.41 (m, 3H), 2.22 - 2.05 (m, 4H), 2.02 (s, 3H).

Example 33





Step 1

To a stirred solution of compound **28-6A** (700 mg, 3.22 mmol) and imidazole (658.09 mg, 9.67 mmol) in DCM (20 mL) was added tert-butylchlorodiphenylsilane (1.50 g, 4.83 mmol) at 0 °C. The reaction was stirred at 20 °C for 4 hours. The reaction was quenched with saturated NH_4Cl solution (30 mL), extracted wtih DCM (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **33-1A**. MS m/z = 456.3 $[M+H]^+$.

With reference to step 1, compound **28-6A** was replaced with compound **28-6B** as the raw material to obtain compound **33-1B**. MS m/z = 456.3 $[M+H]^+$.

Step 2

To a stirred solution of compound **33-1A** (300 mg, 0.66 mmol) in dry THF (5 mL) was added lithium aluminum hydride (37.58 mg, 0.99 mmol) at 0 °C. The reaction was stirred at 0 °C for 0.5 hours. The reaction was quenched with sodium sulfate decahydrate (100 mg). The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **32-2A**. MS m/z = 428.3 $[M+H]^+$.

With reference to step 2, compound **33-1A** was replaced with compound **33-1B** as the raw material to obtain compound **33-2B**. MS m/z = 428.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **33-2A** (100.00 mg, 0.23 mmol) in dry THF (5 mL) was added sodium hydride (46.84 mg, 1.17 mmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (205.49 mg, 0.24 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (6 mL), extracted wtih EtOAc (2 × 6 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **33-3A**. MS m/z = 1227.5 $[M+H]^+$.

With reference to step 3, compound **33-2A** was replaced with compound **33-2B** as the raw material to obtain compound **33-3B**. MS m/z = 1227.5 $[M+H]^+$.

Step 4

To a stirred solution of compound **33-3A** (220 mg, 0.18 mmol) in THF (4 mL) was added tetrabutylammonium fluoride (0.54 mL, 0.54 mmol, 1 M in THF) at 20 °C and the mixture was stirred at 20 °C for 4 hours. The reaction was diluted with EtOAc (20 mL), washed wtih water (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **33-4A**. MS m/z = 989.7 $[M+H]^+$.

With reference to step 4, compound **33-3A** was replaced with compound **33-3B** as the raw material to obtain compound **33-4B**. MS m/z = 989.7 $[M+H]^+$.

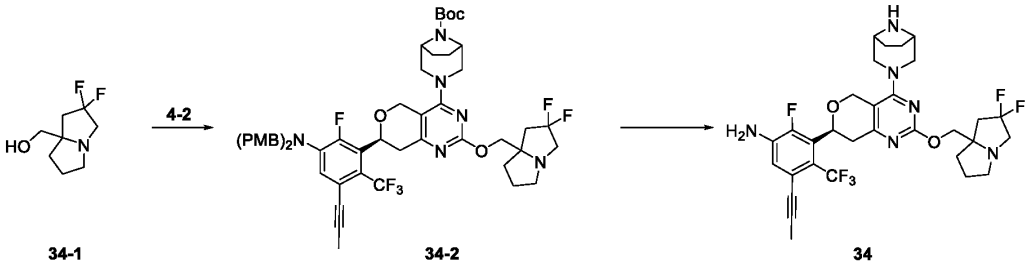
Step 5

The mixture of compound **33-4A** (100 mg, 0.10 mmol) in TFA (3 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **33A**. MS m/z = 649.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.36 (dt, *J* = 56.0, 4.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.77 (m, 1H), 4.66 - 4.62 (m, 1H), 4.23 - 4.13 (m, 2H), 4.11 - 4.04 (m, 1H), 3.59 - 3.40 (m, 7H), 3.25 - 3.16 (m, 1H), 3.08 - 2.92 (m, 2H), 2.91 - 2.80 (m, 2H), 2.49 - 2.38 (m, 1H), 2.24 - 2.16 (m, 1H), 2.09 - 1.99 (m, 5H), 1.96 - 1.77 (m, 4H), 1.74 - 1.63 (m, 2H).

The mixture of compound **33-4B** (140 mg, 0.14 mmol) in TFA (5 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **33B**. MS m/z = 649.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.26 (dt, *J* = 52.0, 4.0 Hz, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz,

1H), 4.82 - 4.77 (m, 1H), 4.68 - 4.61 (m, 1H), 4.35 - 4.29 (m, 1H), 4.22 - 4.15 (m, 2H), 3.84 - 3.77 (m, 1H), 3.73 - 3.67 (m, 1H), 3.57 - 3.49 (m, 3H), 3.46 - 3.34 (m, 2H), 3.25 - 3.02 (m, 4H), 2.89 - 2.81 (m, 1H), 2.49 - 2.39 (m, 1H), 2.08 - 1.92 (m, 6H), 1.91 - 1.79 (m, 4H), 1.77 - 1.64 (m, 2H).

Example 34



34-1 34-2 34

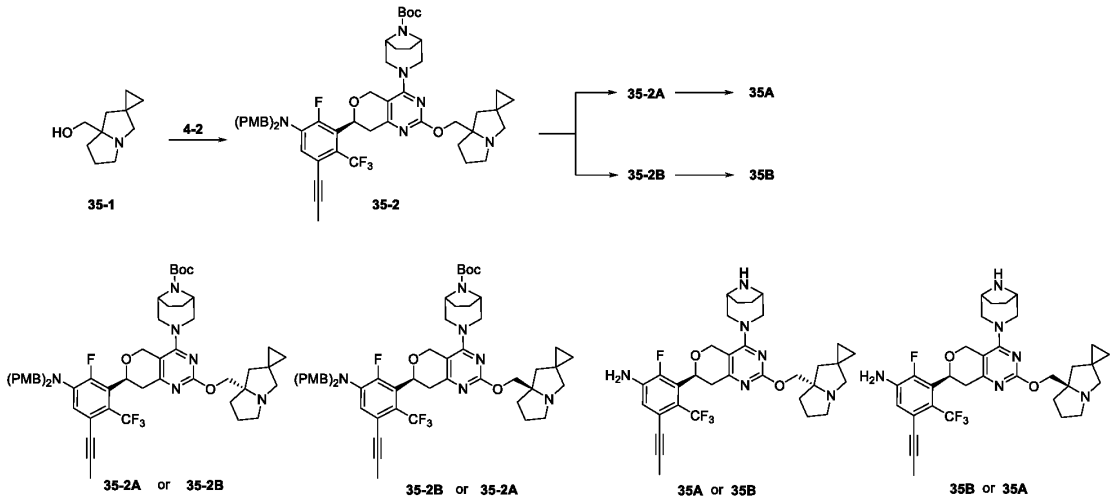
Step 1

To a stirred solution of compound **34-1** (40 mg,0.23 mmol) in dry THF (5 mL) was added sodium hydride (9.03 mg, 0.23 mmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (195.03 mg, 0.23 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **34-2**. MS m/z = 977.5 $[M+H]^+$.

Step 2

The mixture of compound **34-2** (100 mg,0.10 mmol) in TFA (2.5 mL) and DCM (7.5 mL) was stirred at 25 °C for 4 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_4HCO_3); Gradient: (ACN): 50%-70%) to afford compound **34**. MS m/z = 637.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.93 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.16 (m, 1H), 4.85 - 4.82 (m, 1H), 4.72 - 4.69 (m, 1H), 4.24 - 4.11 (m, 3H), 3.93 - 3.88 (m, 2H), 3.71 - 3.66 (m, 1H), 3.59 - 3.54 (m, 1H), 3.47 - 3.38 (m, 1H), 3.30 - 3.31 (m, 4H), 2.92 - 2.83 (m, 2H), 2.62 - 2.50 (m, 1H), 2.37 - 2.27 (m, 1H), 2.22 - 2.12 (m, 2H), 2.05 - 1.98 (m, 6H), 1.94 - 1.85 (m, 3H).

Example 35



Step 1

To a stirred solution of compound **35-1** (48.40 mg, 289.37 μmol) in dry THF (5 mL) was added sodium hydride (41.66 mg, 1.74 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours under nitrogen atmosphere. Then the solution of compound **4-2** (250 mg, 289.37 μmol) in dry THF (2 mL) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was diluted with EtOAc (10 mL), washed wtih brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 30:1) to afford compound **35-2**. MS m/z = 967.8 $[M+H]^+$. The compound **35-2** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®IA, 250*40mm 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: EtOH +(0.2%)(7 M NH_3 in MeOH); Gradient: B% 55%) to afford compound **35-2A** and compound **35-2B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®IA (100*3mm 3μm); Mobile phase: A: Supercritical CO_2; B: (EtOH (0.1% - DEA); Gradient: B% 40%, 8 min). Compound **35-2A**, Rt = 1.847 mins, ee: 100%, MS m/z = 967.8 $[M+H]^+$; compound **35-2B**, Rt = 2.858 mins, ee : 97.95%, MS m/z = 967.8 $[M+H]^+$.

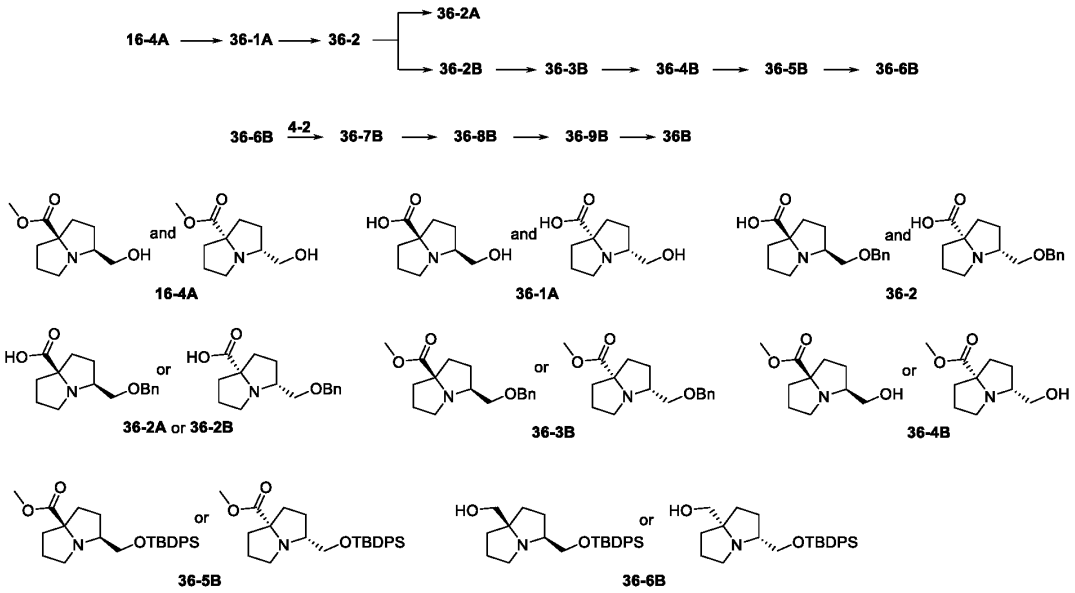
Step 2

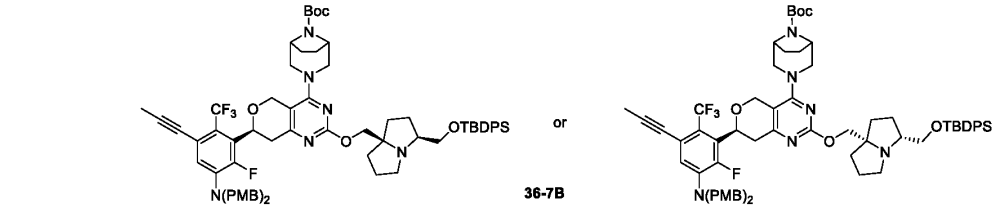
The mixture of compound **35-2A** (70 mg, 72.38 μmol) in TFA (1 mL) and DCM (1 mL) was stirred at 25 °C for 2 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% HCl); Gradient: (ACN): 10%-40%) to afford compound **35A** as HCl salt. MS m/z = 627.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.96 (d, J = 8.0 Hz, 1H), 5.26 - 5.24 (m, 1H), 4.98 - 4.86 (m, 3H), 4.83 - 4.70 (m, 2H), 4.27 - 4.21 (m, 2H), 4.05 - 3.94 (m,

2H), 3.77 - 3.60 (m, 3H), 3.51 - 3.41 (m, 2H), 3.23 - 3.20 (m, 1H), 3.08 - 3.05 (m, 1H), 2.47 - 2.09 (m, 10H), 2.04 (s, 3H), 0.94 - 0.81 (m, 4H).

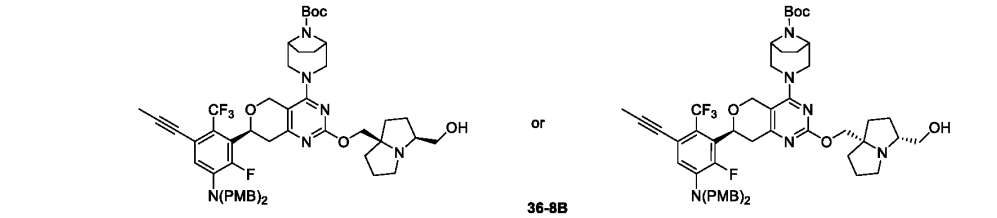
To a solution of compound **35-2B** (73 mg, 75.48 μmol) in DCM (1 mL) was added TFA (1.49 g, 13.07 mmol), the mixture was stirred at 25 °C for 2 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% HCl); Gradient: (ACN): 10%-40%) to afford compound **35B** as HCl salt. MS m/z = 627.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, J = 8.0 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.99 - 4.96 (m, 3H), 4.73 - 4.70 (m, 2H), 4.27 - 4.19 (m, 2H), 4.05 - 3.94 (m, 2H), 3.74 - 3.54 (m, 3H), 3.48 - 3.35 (m, 2H), 3.27 - 3.24 (m, 1H), 3.08 - 3.04 (m, 1H), 2.47 - 2.12 (m, 10H), 2.02 (s, 3H), 0.93 - 0.78 (m, 4H).

Example 36

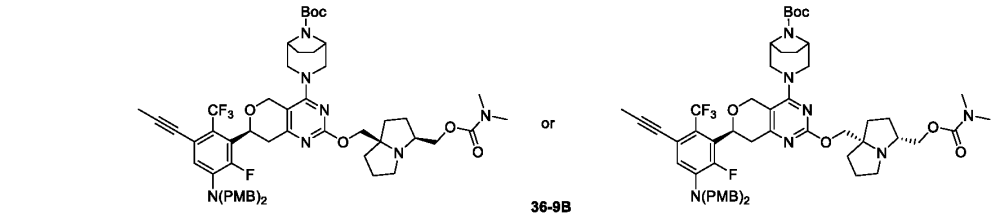




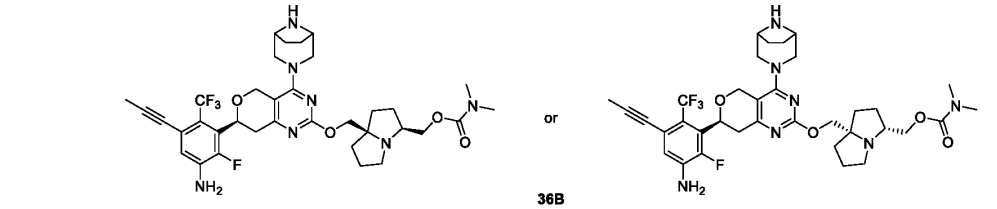
36-7B



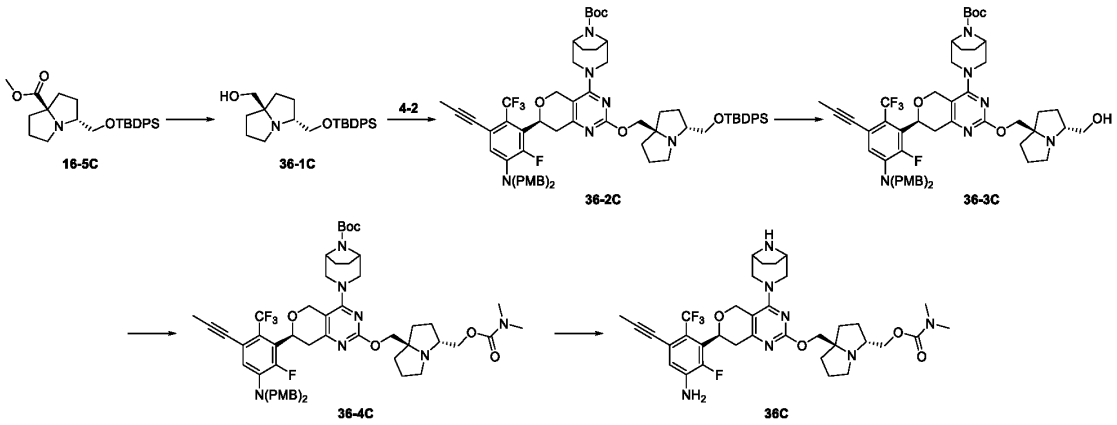
36-8B



36-9B

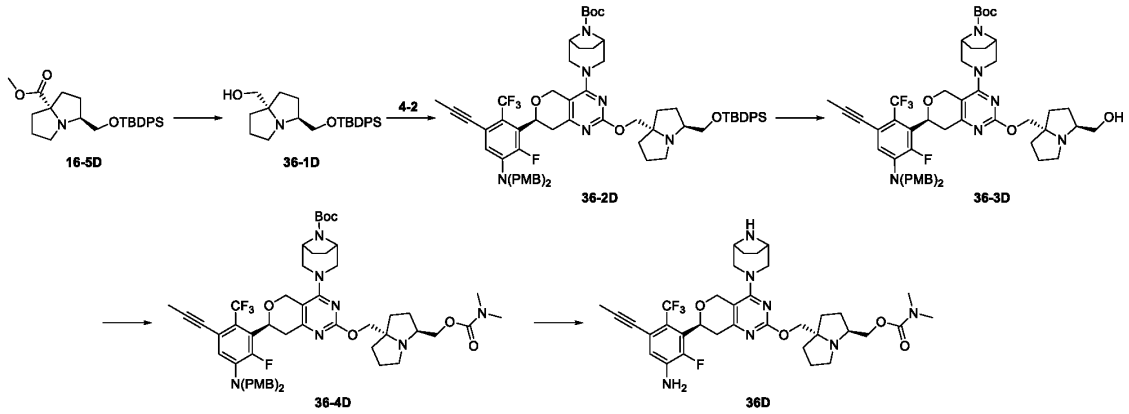


36B



16-5C 36-1C 36-2C 36-3C

36-4C 36C



Step 1

To a stirred solution of compound **16-4A (**2 g, 10.04 mmol) in THF (5 mL) and water (5 mL) was added lithium hydroxide (480.78 mg，20.08 mmol) and the mixture was stirred at 50 °C for 16 hours. The reaction was concentrated under reduced pressure to afford compound **36-1A**. MS m/z = 186.0 $[M+H]^+$.

Step 2

To a stirred solution of compound **36-1A** (300 mg, 1.12 mmol) in N,N-dimethylformamide (5 mL) was added cesium carbonate (2.11 g, 6.48 mmol) and benzyl bromide (738.73 mg, 4.32 mmol) and the mixture was stirred at 25 °C for 8 hours. The reaction was concentrated under reduced pressure to afford crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40 mm, 5 μm, ACN-H_2O (0.05% HCl); Gradient: (ACN): 5%-40%) to afford compound **36-2** as HCl salt. The compound **36-2** was separated by preparative SFC (Column name: UniChiral CND-5H, 20*250 mm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH; Gradient: B% 30%) to afford compound **36-2A** and compound **36-2B**. SFC Analysis methods (chromatographic column: UniChiral CND-5H, 20*250 mm); Mobile phase: A: Supercritical CO_2; B: MeOH; Gradient: B% 30%). Compound **36-2A**, Rt = 2.968 mins, ee: 99.02%, MS m/z = 276.2 $[M+H]^+$; compound **36-2B**, Rt = 3.287 mins, ee : 99.08%, MS m/z = 276.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **36-2B (**700 mg, 2.54 mmol) in DCM (10 mL) was added N,N-dimethylformamide (18.58 mg, 254.23 μmol) at 0 °C. Then thionyl chloride (1.21 g, 10.17 mmol) was added dropwise and the mixture was stirred at 25 °C for 2 hours. The reaction was quenched with MeOH (3 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **36-3B**. MS m/z = 290.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **36-3B (**500 mg, 1.73 mmol) in MeOH (10 mL) was added Pd/C (200 mg, 10% purity) and the mixture was stirred at 25 °C for 4 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was washed with MeOH (20 mL), the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **36-4B**. MS m/z = 200.0 $[M+H]^+$.

Step 5

To a stirred solution of compound **36-4B** (300 mg, 1.51 mmol) in DCM (20 mL) was added imidazole (307.51 mg, 4.52 mmol) and tert-butylchlorodiphenylsilane (620.77 mg, 2.26 mmol). The reaction was stirred at 25 °C for 4 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **36-5B**. MS m/z = 438.1 $[M+H]^+$.

Step 6

To a stirred solution of compound **36-5B** (250 mg, 571.24 μmol) in dry THF (5 mL) was added lithium aluminum hydride (43.36 mg, 1.14 mmol) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with water (2 mL). The reaction was filtered, the filter was washed with acetonitrile (10 mL), the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **36-6B**. MS m/z = 410.1 $[M+H]^+$.

Step 7

To a stirred solution of compound **36-6B** (209.48 mg, 511.39 μmol) in dry THF (5 mL) was added sodium hydride (40.86 mg, 1.02 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **4-2** (300 mg, 340.93 μmol) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (3 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **36-7B**. MS m/z = 1209.9 $[M+H]^+$.

Step 8

To a stirred solution of compound **36-7B** (180 mg, 148.82 μmol) in THF (3 mL) was added tetrabutylammonium fluoride (83.19 mg, 297.65 μmol) and the mixture was stirred at 25 °C for 4 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 5:1) to afford compound **36-8B**. MS m/z = 971.7 $[M+H]^+$.

Step 9

To a stirred solution of compound **36-8B** (100 mg, 102.98 μmol) in THF (3 mL) was added 1,1'-

carbonyldiimidazole (50.09 mg, 308.93 μmol) and the mixture was stirred at 25 °C for 0.5 hours. Then dimethylamine (9.29 mg, 205.95 μmol) was added. The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **36-9B**. MS m/z = 1042.7 $[M+H]^+$.

Step 10

To a solution of compound **36-9B** (80 mg, 76.76 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40 mm, 5μm, ACN-H_2O (0.05% FA); Gradient: (ACN): 10%-40%) to afford compound **36B** as a FA salt. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 (s, 0.38H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0 Hz, 8.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.23 - 4.14 (m, 4H), 4.05 (dd, *J* = 12.0 Hz, 8.0 Hz, 1H), 3.96 (s, 2H), 3.70 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.27 - 3.14 (m, 4H), 3.01 - 2.85 (m, 8H), 2.26 - 2.18 (m, 2H), 2.08 - 1.90 (m, 10H), 1.88 - 1.75 (m, 3H).

Step 11

To a stirred solution of compound **16-5C** (100 mg, 228.50 μmol) in dry THF (2 mL) was added lithium aluminum hydride (17.34 mg, 456.00 μmol) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with water (2 mL). The reaction was filtered, the filter was washed with acetonitrile (10 mL), the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **36-1C**. MS m/z = 410.2 $[M+H]^+$.

With reference to step 11, compound **16-5C** was replaced with compound **16-5D** as the raw material to obtain compound **36-1D**. MS m/z = 410.2 $[M+H]^+$.

Step 12

To a stirred solution of compound **36-1C** (104.74 mg, 255.70 μmol) in dry THF (3 mL) was added sodium hydride (20.00 mg, 510.00 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **4-2** (150 mg, 170.47 μmol) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (2 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **36-2C**. MS m/z = 1209.9 $[M+H]^+$.

With reference to step 12, compound **36-1C** was replaced with compound **36-1D** as the raw material to obtain compound **36-2D**. MS m/z = 1209.9 $[M+H]^+$.

Step 13

To a stirred solution of compound **36-2C** (90 mg, 74.41 μmol) in THF (3 mL) was added tetrabutylammonium fluoride (41.60 mg, 148.83 μmol) and the mixture was stirred at 25 °C for 4 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 5:1) to afford compound **36-3C**. MS m/z = 971.7 $[M+H]^+$.

With reference to step 13, compound **36-2C** was replaced with compound **36-2D** as the raw material to obtain compound **36-3D**. MS m/z = 971.7 $[M+H]^+$.

Step 14

To a stirred solution of compound **36-3C** (200 mg, 205.96 μmol) in THF (3 mL) was added 1,1'-carbonyldiimidazole (100.18 mg, 617.86 μmol) and the mixture was stirred at 25 °C for 0.5 hours. Then dimethylamine (18.58 mg, 411.9 μmol) was added. The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **36-4C**. MS m/z = 1042.7 $[M+H]^+$.

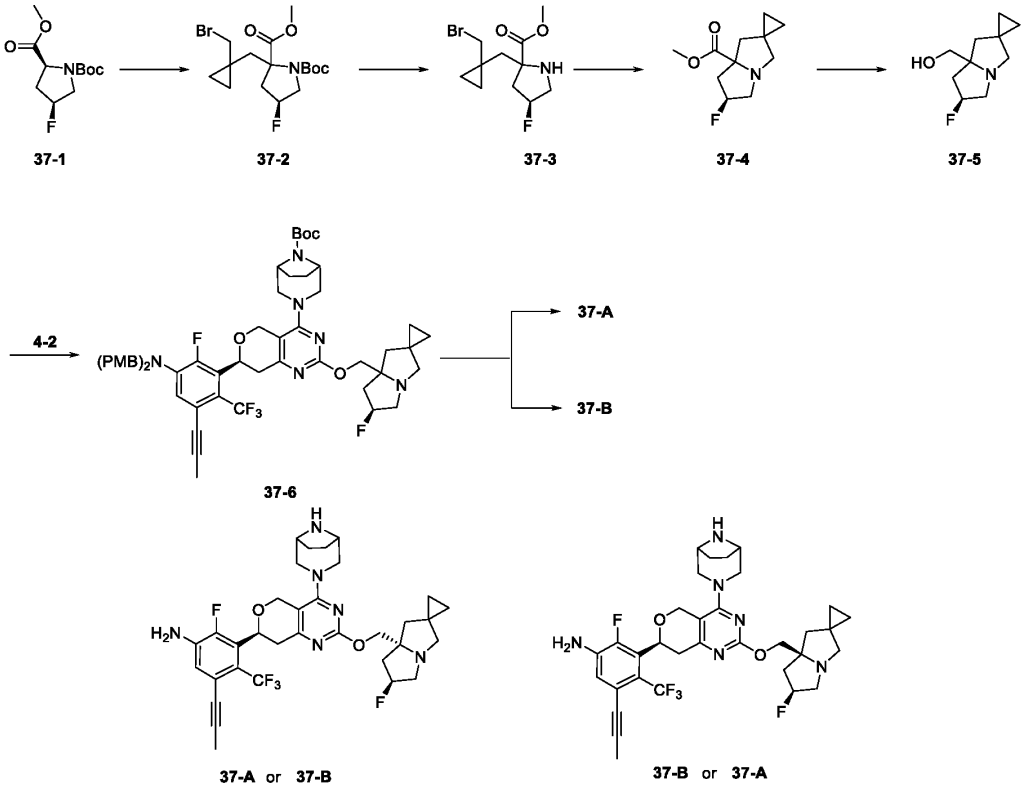
With reference to step 14, compound **36-3C** was replaced with compound **36-3D** as the raw material to obtain compound **36-4D**. MS m/z = 1042.7 $[M+H]^+$.

Step 15

To a solution of compound **36-4C** (80 mg, 76.76 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40 mm, 5μm, ACN-H_2O (0.05% FA); Gradient: (ACN): 10%-40%) to afford compound **36C** as a FA salt. MS m/z = 702.3 $[M+H]^+$. ^1H NMR (400 MHz,CD_3OD) δ ppm 8.53 (s, 0.24 H), 6.90 (d, J = 12.0 Hz, 1H), 5.15 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 4.79 (s, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.40 - 4.31 (m, 3H), 4.26 (t, J = 8.0 Hz, 1H), 4.18 (d, J = 12.0, 1H), 3.83 (s, 1H), 3.71 (s, 2H), 3.61 (d, J = 12.0 Hz, 1H), 3.48 (d, J = 12.0 Hz, 1H), 3.23 (t, J = 8.0 Hz, 2H), 3.11 (d, J = 16.0 Hz, 2H), 2.96 - 2.84 (m, 7H), 2.27 (dd, J = 12.0 Hz, 8.0 Hz, 1H), 2.18 - 2.03 (m, 4H), 2.01 (s, 3H), 1.98 - 1.90 (m, 5H), 1.87 - 1.73 (m, 2H).

With reference to step 15, compound **36-4C** was replaced with compound **36-4D** as the raw material to obtain compound **36D** as a FA salt. MS m/z = 702.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 0.60 H), 6.91 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 4.81 (s, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.44 - 4.40 (m, 2H), 4.37 - 4.31 (m, 2H), 4.22 (d, J = 12.0 Hz, 1H), 3.95 (s, 1H), 3.83 (s, 2H), 3.66 (d, J = 12.0 Hz, 1H), 3.53 (d, J = 12.0 Hz, 1H), 3.34 - 3.33 (m, 1H), 3.29 - 3.15 (m, 3H), 2.97 - 2.86 (m, 7H), 2.32 - 2.20 (m, 2H), 2.16 - 2.08 (m, 3H), 2.03 - 1.90 (m, 9H), 1.87 - 1.79 (m, 1H).

Example 37



Step 1

To a stirred solution of compound **37-1** (5 g, 20.22 mmol) in dry THF (50 mL) was added lithium bis(trimethylsilyl)amide (5.02 g, 30 mmol, 1 M in THF) at -70 °C and the mixture was stirred at -70 °C for 1 hour. Then 1,1-bis-(bromomethyl)-cyclopropane (9.1 g, 39.93 mmol) was added at -70 °C, and the reaction was stirred at 25 °C for 12 hours. The reaction was quenched with saturated NH_4Cl solution (50 mL), extracted wtih EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **37-2**. MS m/z = 294.12 $[M\text{-Boc+H}]^+$.

Step 2

To a stirred solution of compound **37-2** (1.00 g, 2.54 mmol) in DCM (3 mL) was added HCl (5 mL, 4 M in EtOAc) and the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford compound **37-3** as HCl salt. MS m/z = 294.10 $[M+H]^+$.

Step 3

To a stirred solution of compound **37-3** (839.78 mg, HCl salt) in acetonitrile (10 mL) was added potassium carbonate (2.21 g, 15.99 mmol) and the mixture was stirred at 25 °C for 12 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **37-4**.

MS m/z = 214.19 $[M+H]^+$.

Step 4

To a stirred solution of compound **37-4** (570 mg, 2.67 mmol) in dry THF (5 mL) was added lithium aluminum hydride (202.90 mg, 5.35 mmol) under nitrogen atmosphere. The reaction was stirred at 25 °C for 2 hours. The reaction was diluted with water (10 mL), extracted wtih EtOAc (30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **37-5**. MS m/z = 186.24 $[M+H]^+$.

Step 5

To a stirred solution of compound **37-5** (100 mg, 0.53 mmol) in dry THF (10 mL) was added sodium hydride (110 mg, 4.58 mmol, 60% purity) and the mixture was stirred at 25 °C for 0.5 hours under nitrogen atmosphere. Then the solution of compound **4-2** (300 mg, 0.34 mmol) in dry THF (1 mL) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was diluted with EtOAc (20 mL), washed wtih brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **37-6**. MS m/z = 985.8 $[M+H]^+$.

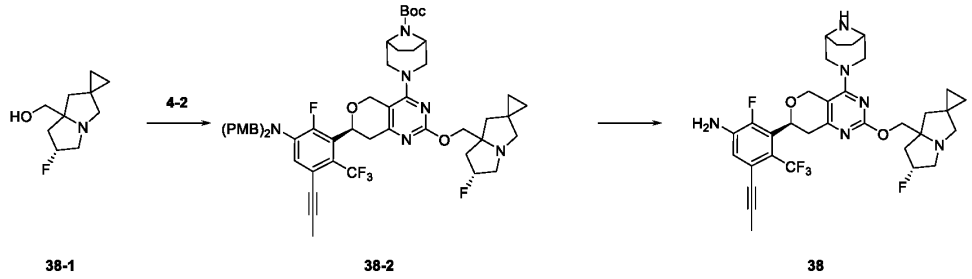
Step 6

To a solution of compound **37-6** (250 mg, 0.25 mmol) in DCM (10 mL) was added TFA (2 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% HCl); Gradient: (ACN): 10%-40%) to afford compound **37A** as HCl salt and compound **37B** as HCl salt. HPLC Analysis methods (chromatographic column: Waters Xbridge C18，50mm×4.6mm×3.5μm; Mobile phase: A: H_2O (0.1% NH_4HCO_3); B: ACN; Gradient: B%: 0-0%, 1.5 min；0-85%, 4.0 min; 85-85%, 4.49 min; 85-0%, 0.01 min). Compound **37A**, Rt = 5.868 mins; compound **37B**, Rt = 6.003 mins.

Compound **37A** HCl salt: MS m/z = 645.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.02 (d, *J* = 8.0 Hz, 1H), 5.61 (d, *J* = 52.0 Hz, 1H), 5.27 - 5.25 (m, 1H), 5.06 - 4.98 (m, 3H), 4.82 - 4.74 (m, 2H), 4.7 - 4.19 (m, 3H), 4.03 (s, 2H), 3.95 - 3.92 (m, 1H), 3.77 - 3.63 (m, 2H), 3.48 - 3.36 (m, 1H), 3.13 - 3.09 (m, 2H), 2.87 - 2.57 (m, 3H), 2.22 - 2.03 (m, 7H), 1.89 - 1.86 (m, 1H), 0.98 - 0.94 (m, 2H), 0.79 - 0.75 (m, 2H).

Compound **37B** HCl salt: MS m/z = 645.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.95 (d, *J* = 8.0 Hz, 1H), 5.73 - 5.60 (m, 1H), 5.26 - 5.24 (m, 1H), 5.12 - 4.98 (m, 5H), 4.36 - 4.20 (m, 3H), 4.02 (s, 2H), 3.89 - 3.85 (m, 1H), 3.69 - 3.66 (m, 1H), 3.57 - 3.54 (m, 1H), 3.40 (m, 1H), 3.13 - 2.67 (m, 5H), 2.30 - 2.13 (m, 5H), 2.02 (s, 3H), 0.91-0.88 (m, 4H).

Example 38



Step 1

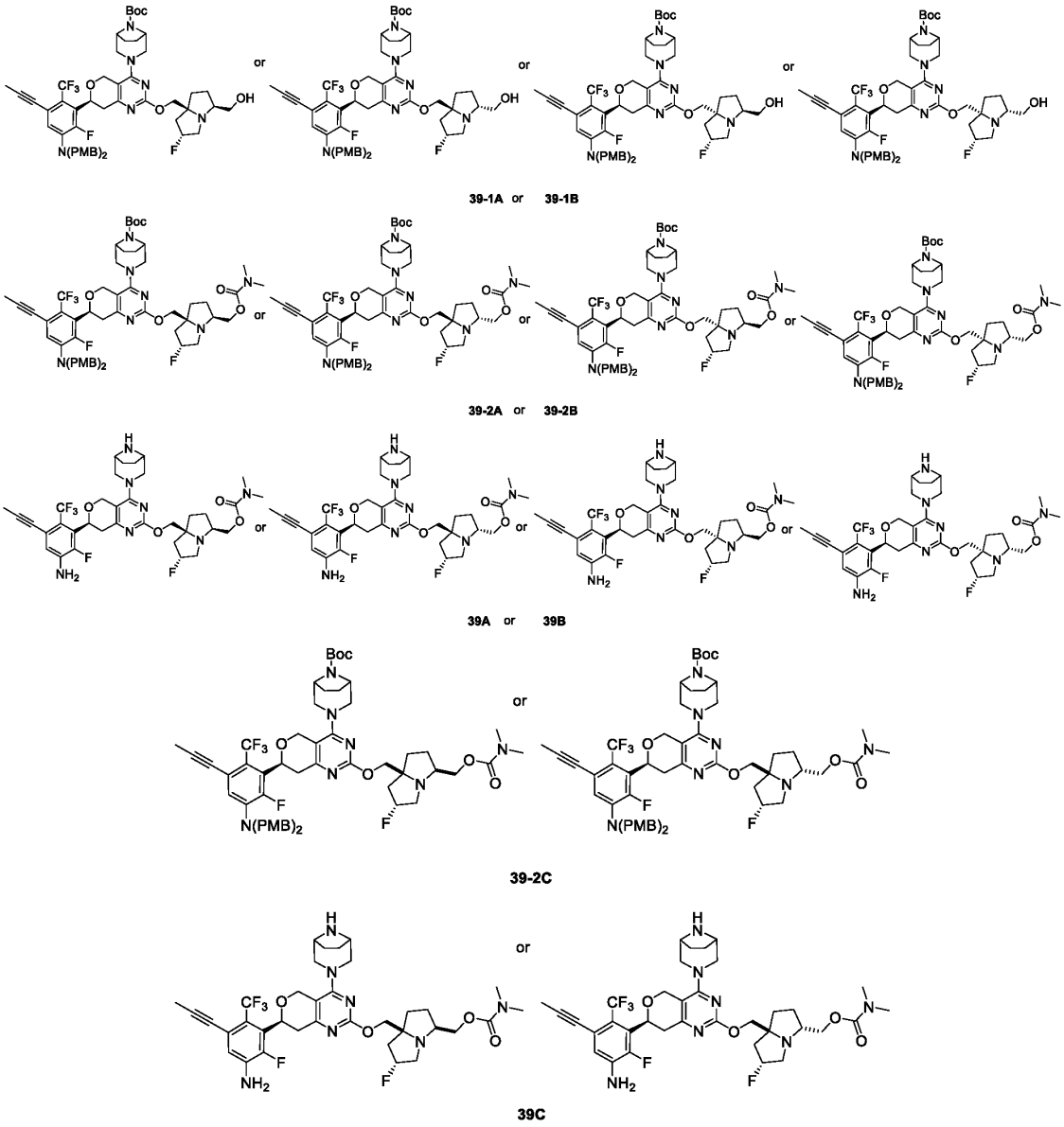
To a stirred solution of compound **38-1** (100 mg, 0.54 mmol) in dry THF (5 mL) was added sodium hydride (65 mg, 2.70 mmol, 60% purity) and the mixture was stirred at 25 °C for 0.5 hours under nitrogen atmosphere. Then the solution of compound **4-2** (373 mg, 0.44 mmol) in dry THF (1 mL) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was diluted with EtOAc (20 mL), washed wtih brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **38-2**. MS m/z = 985.8 $[M+H]^+$.

Step 2

To a solution of compound **38-2** (180 mg, 0.18 mmol) in DCM (10 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% HCl); Gradient: (ACN): 10%-40%) to afford compound **38** as HCl salt. MS m/z = 645.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.95 (d, *J* = 8.0 Hz, 1H), 5.62 (d, *J* = 52.0 Hz, 1H), 5.23 (d, *J* = 8.0 Hz, 1H), 5.04 - 4.87 (m, 5H), 4.30 - 4.11 (m, 3H), 4.07 - 3.93 (m, 3H), 3.78 -3.58 (m, 1H), 3.64 - 3.55 (m, 1H), 3.46 - 3.39 (m, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.06 (d, *J* = 16.0 Hz, 1H), 2.86 - 2.79 (m, 2H), 2.71 - 2.57 (m, 1H), 2.15 (s, 3H), 2.06 - 1.99 (m, 4H), 1.90 (d, *J* = 12.0 Hz, 1H), 0.99 - 0.92 (m, 2H), 0.85 - 0.69 (m, 2H).

Example 39





39-1A or 39-1B

39-2A or 39-2B

39A or 39B

39-2C

39C

Step 1

To a stirred solution of tetrabutylammonium fluoride (0.5 mL, 1 M in THF) was added the compound **33-3A** (20 mg, 16.29 μmol) and the mixture was stirred at 25 °C for 2 hours. The reaction was diluted with water (10 mL), extracted with EtOAc (3 × 3 mL). The combined organic layers were washed wtih brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **39-1A** and compound **39-1B**. compound **39-1A**, MS m/z = 989.7 $[M+H]^+$, (DCM:MeOH = 20:1, Rf = 0.18). compound **39-1B**, MS m/z = 989.7 $[M+H]^+$, (DCM:MeOH = 20:1, Rf = 0.14).

Step 2

To a stirred solution of compound **39-1A** (30 mg, 30.33 μmol) in THF (2 mL) was added 1,1'-carbonyldiimidazole (14.75 mg, 90.99 μmol) and the mixture was stirred at 25 °C for 30 minutes. Then dimethylamine (2.05 mg, 45.49 μmol) was added. The resulting mixture was stirred at 25 °C for 3 hours. The reaction was quenched with saturated NH_4Cl solution (5 mL), extracted wtih EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **39-2A**. MS m/z = 1060.7 $[M+H]^+$.

With reference to step 2, compound **39-1A** was replaced with compound **39-1B** as the raw material to obtain compound **39-2B**. MS m/z = 1060.7 $[M+H]^+$.

With reference to step 2, compound **39-1A** was replaced with compound **39-1C** as the raw material to obtain compound **39-2C**. MS m/z = 1060.7 $[M+H]^+$.

Step 3

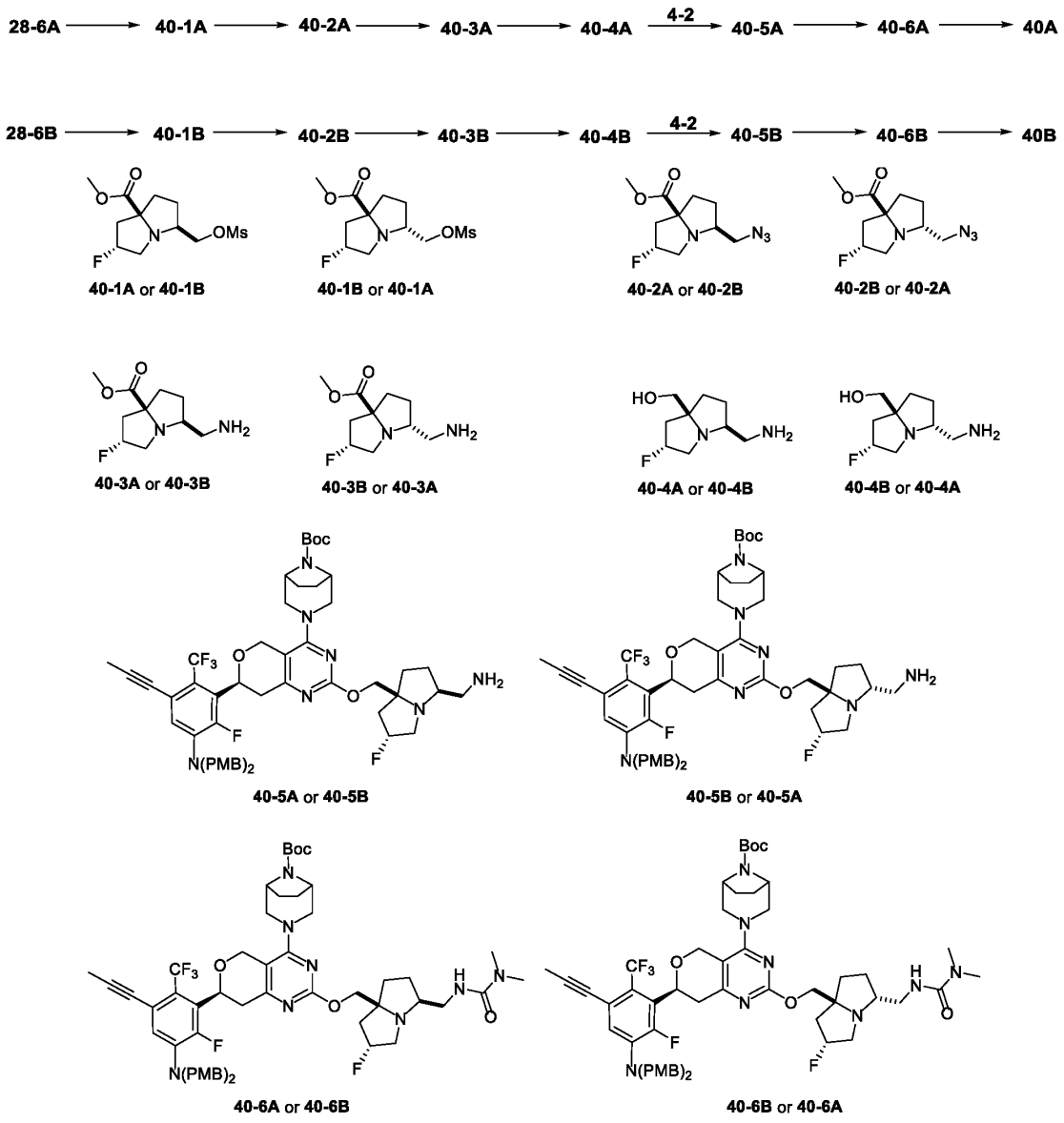
To a solution of compound **39-2A** (20 mg, 17.63 μmol) in DCM (1 mL) was added TFA (0.5 mL), the mixture was stirred at 20 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40mm*5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 20%-40%) to afford compound **39A** as FA salt. MS m/z = 720.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 2.87H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.445.11 (m, 2H), 4.81 - 4.79 (m, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.11 (s, 2H), 4.02 - 3.93 (m, 3H), 3.88 - 3.84 (m, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 3.55 (d, *J* = 12.0 Hz, 1H), 3.30 - 3.15 (m, 4H), 3.06 - 2.84 (m, 8H), 2.28 - 2.09 (m, 4H), 2.07 - 1.86 (m, 9H).

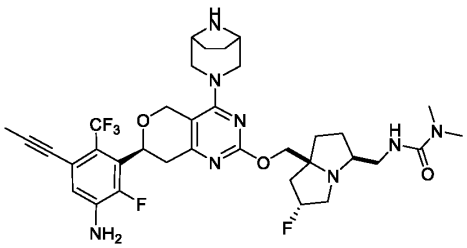
To a solution of compound **39-2B** (20 mg, 17.63 μmol) in DCM (1 mL) was added TFA (0.5 mL), the mixture was stirred at 20 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40mm*5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 20%-40%) to afford compound **39B** as FA salt. MS m/z = 720.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 2.90H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.48 - 5.28 (m, 1H), 5.23 - 5.09 (m, 1H), 4.81 - 4.79 (s, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.09 (m, 2H), 4.08 - 4.04 (m, 1H), 4.01-3.96 (m, 1H), 3.94 - 3.88 (m, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.59 (d, *J* = 16.0 Hz, 1H), 3.50 - 3.41 (m, 1H), 3.29 - 3.19 (m, 3H), 3.08 - 2.84 (m, 9H), 2.47 - 2.38 (m, 1H), 2.28 - 2.19 (m, 2H), 2.09 - 2.00 (m, 5H), 1.99 - 1.79 (m, 4H), 1.76 - 1.66 (m, 1H).

The solution of compound **39-2C** (200 mg, 188.65 μmol) in TFA (5 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3);

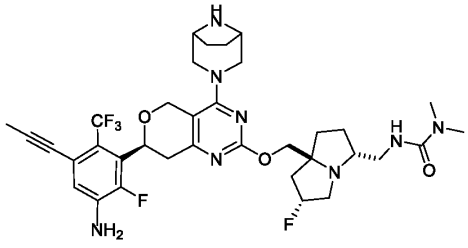
Gradient: (ACN): 50%-70%) to afford compound **39C**. MS m/z = 720.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.34 - 5.20 (m, 1H), 5.16 - 5.12 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 4.82 - 4.78 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.34 - 4.19 (m, 5H), 3.57 - 3.41 (m, 5H), 3.24 - 3.10 (m, 3H), 3.06 - 2.92 (m, 7H), 2.85 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 2.49 - 2.40 (m, 1H), 2.11 - 1.98 (m, 6H), 1.92 - 1.79(m, 4H), 1.76 - 1.65(m, 2H).

Example 40





40A or 40B



40B or 40A

Step 1

To a stirred solution of compound **28-6A** (420 mg, 1.93 mmol) in DCM (10 mL) was added triethyl amine (586.91 mg, 5.80 mmol) and methanesulfonyl chloride (332.21 mg, 2.90 mmol). The mixture was stirred at 25 °C for 2 hours. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **40-1A**. MS m/z = 296.1 $[M+H]^+$.

With reference to step 1, compound **28-6A** was replaced with compound **28-6B** as the raw material to obtain compound **40-1B**. MS m/z = 296.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **40-1A** (405 mg, 1.37 mmol) in N,N-dimethylformamide (10 mL) was added sodium azide (178.30 mg, 2.74 mmol) and the mixture was stirred at 80 °C for 16 hours. The reaction was concentrated under reduced pressure to afford compound **40-2A**. MS m/z = 243.1 $[M+H]^+$.

With reference to step 2, compound **40-1A** was replaced with compound **40-1B** as the raw material to obtain compound **40-2B**. MS m/z = 243.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **40-2A** (250 mg, 1.03 mmol) in MeOH (10 mL) was added Pd/C (109.82 mg, 1.03 mmol) and the mixture was stirred at 25 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford compound **40-3A**. MS m/z = 217.2 $[M+H]^+$.

With reference to step 3, compound **40-2A** was replaced with compound **40-2B** as the raw material to obtain compound **40-3B**. MS m/z = 217.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **40-3A** (180 mg, 832.36 μmol) in dry THF (10 mL) was added lithium aluminum hydride (1 M, 2.5 mL) at 0 °C. The reaction was stirred at 0 °C for 2 hours. The reaction was quenched with water (0.1 mL). Then anhydrous Na_2SO_4 (0.5 g) was added and stirred for 2 minutes. The resulting mixture was filtered through a celite, the filter was washed with THF (20

mL). The filtrate was concentrated under reduced pressure to afford compound **40-4A**. MS m/z = 189.2 $[M+H]^+$.

With reference to step 4, compound **40-3A** was replaced with compound **40-3B** as the raw material to obtain compound **40-4B**. MS m/z = 189.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **40-4A** (105 mg, 557.79 μmol) in dry N,N-dimethylformamide (3 mL) was added sodium hydride (66.93 mg, 1.67 mmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours under nitrogen atmosphere. Then compound **4-2** (490.83 mg, 557.79 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (15 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **40-5A**. MS m/z = 988.7 $[M+H]^+$.

With reference to step 5, compound **40-4A** was replaced with compound **40-4B** as the raw material to obtain compound **40-5B**. MS m/z = 988.7 $[M+H]^+$.

Step 6

To a stirred solution of compound **40-5A** (140 mg, 141.69 μmol) in THF (10 mL) was added 1,1'-carbonyldiimidazole (45.95 mg, 283.37 μmol) and the mixture was stirred at 25 °C for 1 hour. Then dimethylamine (2 M in THF, 14.74 μL) was added. The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (H_2O:ACN = 3:2) to afford compound **40-6A**. MS m/z = 1059.7 $[M+H]^+$.

With reference to step 6, compound **40-5A** was replaced with compound **40-5B** as the raw material to obtain compound **40-6B**. MS m/z = 1059.7 $[M+H]^+$.

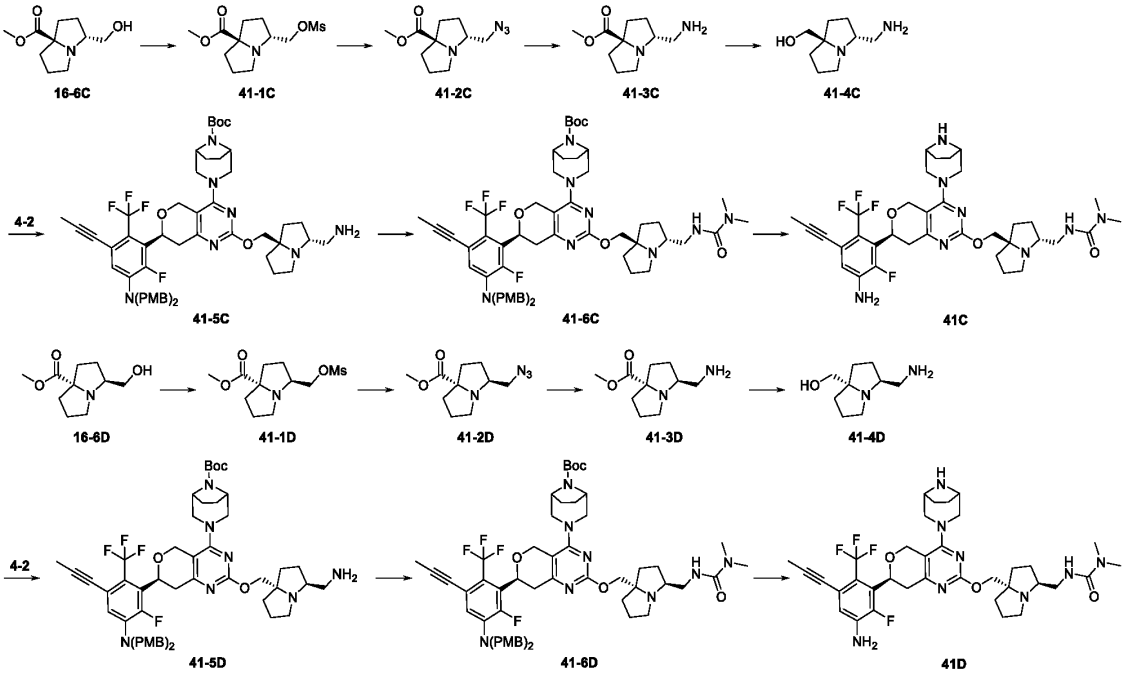
Step 7

To a solution of compound **40-6A** (50 mg, 47.21 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-75%) to afford compound **40A**. MS m/z = 719.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.36 - 5.03 (m, 2H), 4.81 - 4.77 (m, 2H), 4.68 - 4.55 (m, 2H), 4.27-4.16 (m, 2H), 3.94 - 3.89 (m, 1H), 3.58- 3.42 (m, 5H), 3.23 - 3.10 (m, 2H), 3.06 (d, J = 12.0 Hz, 1H), 3.00 - 2.91 (m, 1H), 2.88 (s, 6H), 2.85 - 2.82 (m, 1H), 2.21 - 2.13 (m, 2H), 2.04 - 1.99 (m, 5H), 1.87 - 1.60 (m, 6H).

To a solution of compound **40-6B** (50 mg, 47.21 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure.

The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-75%) to afford compound **40B** as FA salt. MS m/z = 719.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.47 (s, 1.3H), 6.95 - 6.82 (m, 1H), 5.48 - 5.35 (m, 1H), 5.21 - 5.07 (m, 2H), 4.76 - 4.70 (m, 1H), 4.66 - 4.51 (m, 2H), 4.46 - 4.32 (m, 2H), 4.25 - 4.06 (m, 2H), 4.04 - 3.99 (m, 2H), 3.64 - 3.56 (m, 1H), 3.52 - 3.46 (m, 1H), 3.43 - 3.34 (m, 2H), 3.30 - 3.23 (m, 2H), 3.11 - 3.05 (m, 1H), 2.94 - 2.89 (m, 6H), 2.62 - 2.16 (m, 4H), 2.08 - 1.97 (m, 7H), 1.94 - 1.89 (m, 2H).

Example 41



Step 1

To a stirred solution of compound **16-6C** (216 mg, 1.08 mmol) and triethyl amine (438.79 mg, 4.34 mmol) in DCM (3 mL) was added methanesulfonyl chloride (248.37 mg, 2.17 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 hours. The reaction was quenched with water (15 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **41-1C**. MS m/z = 278.0 $[M+H]^+$.

With reference to step 1, compound **16-6C** was replaced with compound **16-6D** as the raw material to obtain compound **41-1D**. MS m/z = 278.0 $[M+H]^+$.

Step 2

To a stirred solution of compound **41-1C** (300.7 mg, 1.08 mmol) in N,N-dimethylformamide (5

mL) was added sodium azide (211.46 mg, 3.25 mmol) and the mixture was stirred at 80 °C for 16 hours. The reaction was concentrated under reduced pressure to afford compound **41-2C**. MS m/z = 225.0 $[M+H]^+$.

With reference to step 2, compound **41-1C** was replaced with compound **41-1D** as the raw material to obtain compound **41-2D**. MS m/z = 225.0 $[M+H]^+$.

Step 3

To a stirred solution of compound **41-2C** (243.0 mg, crude) in MeOH (5 mL) was added Pd/C (230.6 mg, 216.71 mmol, 10% purity) and the mixture was stirred at 25 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was washed with MeOH (3 × 15 mL). The filtrate was concentrated under reduced pressure to afford crude compound **41-3C**. MS m/z = 199.0 $[M+H]^+$.

With reference to step 3, compound **41-2C** was replaced with compound **41-2D** as the raw material to obtain compound **41-3D**. MS m/z = 199.0 $[M+H]^+$.

Step 4

To a stirred solution of compound **41-3C** (214.8 mg, crude) in dry THF (5 mL) was added lithium aluminum hydride (866.73 μL, 2.17 mmol, 2.5 M) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with water (0.3 mL), filtered, the filter was EtOAc (3 × 15 mL). The filtrate was concentrated under reduced pressure to afford crude compound **41-4C**. MS m/z = 171.0 $[M+H]^+$.

With reference to step 4, compound **41-3C** was replaced with compound **41-3D** as the raw material to obtain compound **41-4D**. MS m/z = 171.0 $[M+H]^+$.

Step 5

To a stirred solution of compound **41-4C** (184.5 mg, crude) in dry THF (5 mL) was added sodium hydride (86.69 mg, 2.17 mmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours under nitrogen atmosphere. Then compound **4-2** (1.14 g, 1.30 mmol) was added, and the reaction was stirred at 0 °C for 1 hour. The reaction was quenched with water (0.5 mL), extracted wtih DCM (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (ACN:H_2O = 2:3) to afford compound **41-5C**. MS m/z = 970.0 $[M+H]^+$.

With reference to step 5, compound **41-4C** was replaced with compound **41-4D** as the raw material to obtain compound **41-5D**. MS m/z = 970.0 $[M+H]^+$.

Step 6

To a stirred solution of compound **41-5C** (183 mg, 188.64 μmol) in THF (3 mL) was added 1,1'-carbonyldiimidazole (61.18 mg, 377.28 mmol) and the mixture was stirred at 25 °C for 2 hours. Then dimethylamine (2 M in THF, 141.49 μL, 282.99 μmol) was added. The resulting mixture was stirred

at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (ACN:H_2O = 2:3) to afford compound **41-6C**. MS m/z = 1041.8 $[M+H]^+$.

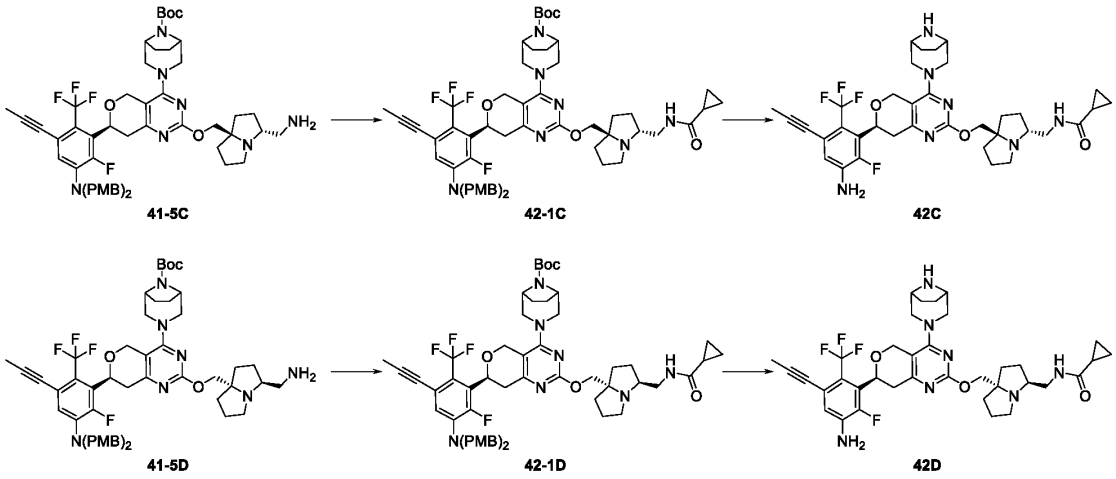
With reference to step 6, compound **41-5C** was replaced with compound **41-5D** as the raw material to obtain compound **41-6D**. MS m/z = 1041.8 $[M+H]^+$.

Step 7

To a solution of compound **41-6C** (90 mg, 86.44 μmol) in DCM (1.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge C18, 250*19mm, 5μm, ACN-H_2O (0.05% NH_3); Gradient: (ACN): 45%-70%) to afford compound **41C**. MS m/z = 701.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 6.88 (d, J = 8.0 Hz, 1H), 6.18 (t, J = 4.0 Hz, 1H), 6.01 (s, 2H), 5.02 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.74 (d, J = 16.0 Hz, 1H), 4.54 (d, J = 16.0 Hz, 1H), 3.92 - 3.83 (m, 3H), 3.39 - 3.32 (m, 5H), 3.23 (d, J = 12.0 Hz, 1H), 3.17 - 3.10 (m, 1H), 3.06 - 2.99 (m, 2H), 2.86 (d, J = 12.0 Hz, 1H), 2.81 - 2.75 (m, 8H), 2.63 - 2.57 (m, 1H), 2.03 (s, 3H), 2.00 - 1.97 (m, 1H), 1.81 - 1.75 (m, 1H), 1.70 - 1.51 (m, 9H), 1.47 - 1.41 (m, 1H).

To a solution of compound **41-6D** (30 mg, 28.81 μmol) in DCM (1.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-75%) to afford compound **41D** as FA salt. MS m/z = 701.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3CN) δ ppm 8.10 (s, 0.13H), 6.91 (d, J = 8.0 Hz, 1H), 5.14 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.10 - 4.07 (m, 3H), 4.00 - 3.94 (m, 1H), 3.71 (d, J = 16.0 Hz, 1H), 3.60 - 3.56 (m, 2H), 3.49 (dd, J = 16.0 Hz, 8.0 Hz, 1H), 3.42 - 3.32 (m, 2H), 3.24 - 3.09 (m, 2H), 2.87 (dd, J = 16.0 Hz, 4.0 Hz, 1H), 2.79 (s, 6H), 2.20 - 2.15 (m, 4H), 2.12 - 2.03 (m, 9H), 1.90 - 1.83 (m, 2H).

Example 42



Step 1

To a stirred solution of cyclopropanecarboxylic acid (6.66 mg, 77.31 μmol) in DCM (3 mL) was added N,N-diisopropylethylamine (19.98 mg, 154.62 μmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (29.4 mg, 77.31 μmol). The mixture was stirred at 25 °C for 0.5 hours. Then compound **41-5C** (50 mg, 51.54 μmol) was added and the resulting mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 15:1) to afford compound **42-1C**. MS m/z = 1038.8 $[M+H]^+$.

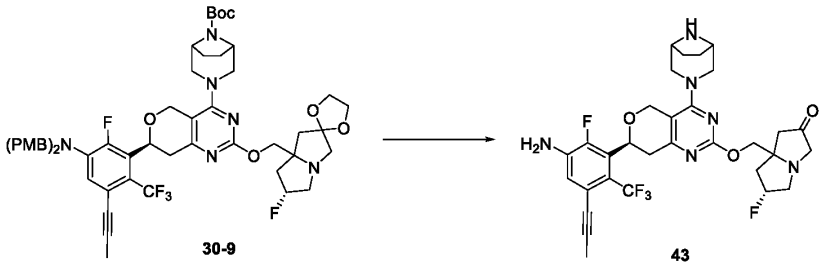
With reference to step 1, compound **41-5C** was replaced with compound **41-5D** as the raw material to obtain compound **42-1D**. MS m/z = 1038.8 $[M+H]^+$.

Step 2

To a solution of compound **42-1C** (25 mg, 24.08 μmol) in DCM (1.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: SunFire C18, 150*40mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 6%-36%) to afford compound **42C**. MS m/z = 698.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.14 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.77 (s, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.33 (d, J = 12.0 Hz, 1H), 4.12 (d, J = 12.0 Hz, 2H), 3.57 - 3.51 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.25 - 3.17 (m, 2H), 3.05 (d, J = 16.0 Hz, 2H), 2.96 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 2.90 - 2.82 (m, 2H), 2.62 - 2.58 (m, 1H), 2.04 - 1.98 (m, 6H), 1.92 - 1.83 (m, 6H), 1.76 - 1.71 (m, 2H), 1.62 - 1.56 (m, 2H), 0.85 - 0.81 (m, 2H), 0.75 - 0.72 (m, 2H).

To a solution of compound **42-1D** (25 mg, 24.08 μmol) in DCM (1.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: SunFire C18, 150*40mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 10%-36%) to afford compound **42D** as FA salt. MS m/z = 698.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.49 (s, 2.55H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.84 (s, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 16.0 Hz, 1H), 3.96 - 3.86 (m, 3H), 3.73 - 3.67 (m, 2H), 3.58 (d, *J* = 16.0 Hz, 1H), 3.52 - 3.47 (m, 2H), 3.28 - 3.20 (m, 3H), 2.91 (dd, *J* = 20.0 Hz, 4.0 Hz, 1H), 2.34 - 2.30 (m, 1H), 2.26 - 2.14 (m, 4H), 2.08 - 1.95 (m, 9H), 1.89 - 1.85 (m, 1H), 1.61 - 1.55 (m, 1H), 0.89 - 0.85 (m, 2H), 0.81 - 0.76 (m, 2H).

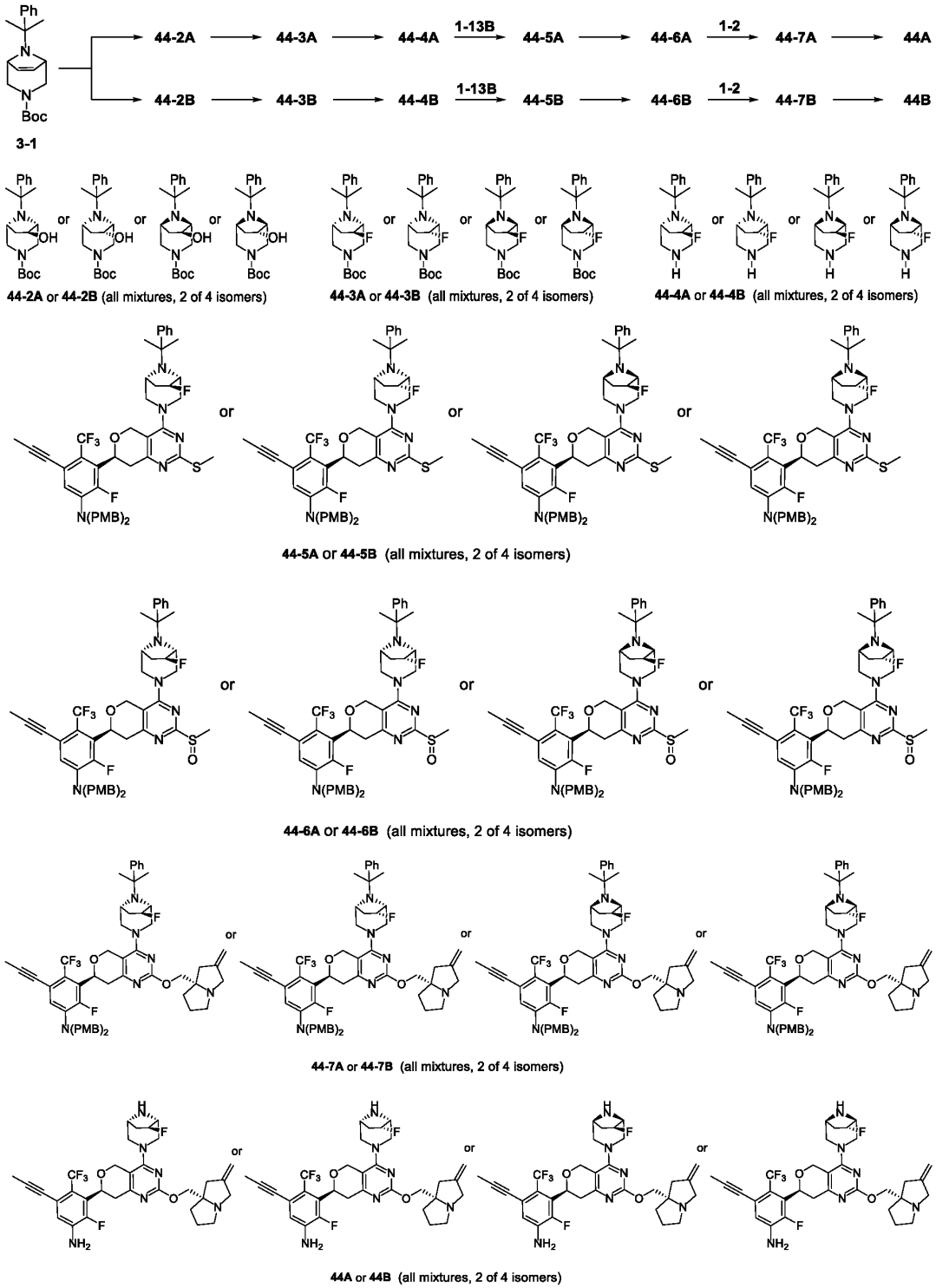
Example 43



Step 1

To a solution of compound **30-9** (100 mg, 0.10 mmol) in dry THF (3 mL) was added water (1.5 mL) and concentrated HCl (1.5 mL) sequentially at 25 °C. The mixture was stirred at 75 °C for 32 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_4HCO_3); Gradient: (ACN): 50%-70%) to afford compound **43**. MS m/z = 633.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) *δ* ppm 6.96 (d, *J* = 8.0 Hz, 1H), 5.45 - 5.30 (m, 1H), 5.22 - 5.18 (m, 1H), 4.87 - 4.84 (m, 1H), 4.73 - 4.70 (m, 1H), 4.40 - 4.32 (m, 2H), 4.23 - 4.18 (m, 1H), 3.79 - 3.73 (m, 2H), 3.66 - 3.50 (m, 4H), 3.32 - 3.24 (m, 2H), 3.17 - 3.04 (m, 2H), 2.94 - 2.88 (m, 1H), 2.77 - 2.71 (m, 1H), 2.62 - 2.57 (m, 1H), 2.50 - 2.47 (m, 1H), 2.43 - 2.34 (m, 1H), 2.16 - 2.11 (m, 1H), 2.07 (s, 3H), 1.97 - 1.91 (m, 2H), 1.85 - 1.80 (m, 1H).

Example 44



Step 1

To a stirred solution of compound **3-1** (4 g, 12.18 mmol) in THF (40 mL) was added borane-tetrahydrofuran complex (3.14 g, 36.54 mmol, 1 M) and the mixture was stirred at 60 °C for 1.5

hours. Then sodium hydroxide (2 M, 1.95 g, 48.71 mmol) and hydrogen peroxide (6.90 g, 60.89 mmol) was added. The resulting mixture was stirred at 25 °C for 3 hours. The reaction was quenched with water (50 mL), extracted wtih EtOAc (3 × 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **44-2A** and compound **44-2B**. compound **44-2A**, MS m/z = 347.2 $[M+H]^+$, (PE:EtOAc = 5:1, Rf = 0.5). compound **44-2B**, MS m/z = 347.2 $[M+H]^+$, (PE:EtOAc = 5:1, Rf = 0.3).

Step 2

To a stirred solution of compound **44-2A** (1 g, 2.89 mmol) in DCM (30 mL) was added diethylaminosulfur trifluoride (1.4 g, 8.66 mmol) and the mixture was stirred at 0 °C for 1 hour. The reaction was quenched with saturated $NaHCO_3$ solution (50 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **44-3A**. MS m/z = 349.1 $[M+H]^+$.

With reference to step 2, compound **44-2A** was replaced with compound **44-2B** as the raw material to obtain compound **44-3B**. MS m/z = 349.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **44-3A** (200mg, 574.0 μmol) in MeOH (2 mL) was added diluted HCl (2 mL, 1 M) and the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure to afford compound **44-4A**. MS m/z = 249.2 $[M+H]^+$.

With reference to step 3, compound **44-3A** was replaced with compound **44-3B** as the raw material to obtain compound **44-4B**. MS m/z = 249.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **44-4A** (140 mg, 563.75 μmol) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (72.86 mg, 563.75 μmol) and **1-13B** (443 mg, 563.75 μmol). The resulting mixture was stirred at 100 °C for 1 hour. The reaction was quenched with water (2 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **44-5A**. MS m/z = 884.5 $[M+H]^+$.

With reference to step 4, compound **44-4A** was replaced with compound **44-4B** as the raw material to obtain compound **44-5B**. MS m/z = 884.5 $[M+H]^+$.

Step 5

To a stirred solution of compound **44-5A** (260 mg，294.11 μmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (50.75 mg, 294.11 μmol, 85% purity) and the mixture was stirred at 25 °C for 2 hours. The reaction was quenched with saturated solution of sodium sulfite (2 mL), extracted wtih DCM (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution

(5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **44-6A**. MS m/z = 900.6 $[M+H]^+$.

With reference to step 5, compound **44-5A** was replaced with compound **44-5B** as the raw material to obtain compound **44-6B**. MS m/z = 900.6 $[M+H]^+$.

Step 6

To a stirred solution of (S)-(2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (66.4 mg, 433.3 μmol) in dry THF (5 mL) was added sodium hydride (20.8 mg, 866.66 μmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours. Then compound **44-6A** (260 mg, 289.0 μmol) was added and the resulting mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **44-7A**. MS m/z = 989.7 $[M+H]^+$.

With reference to step 6, compound **44-6A** was replaced with compound **44-6B** as the raw material to obtain compound **44-7B**. MS m/z = 989.7 $[M+H]^+$.

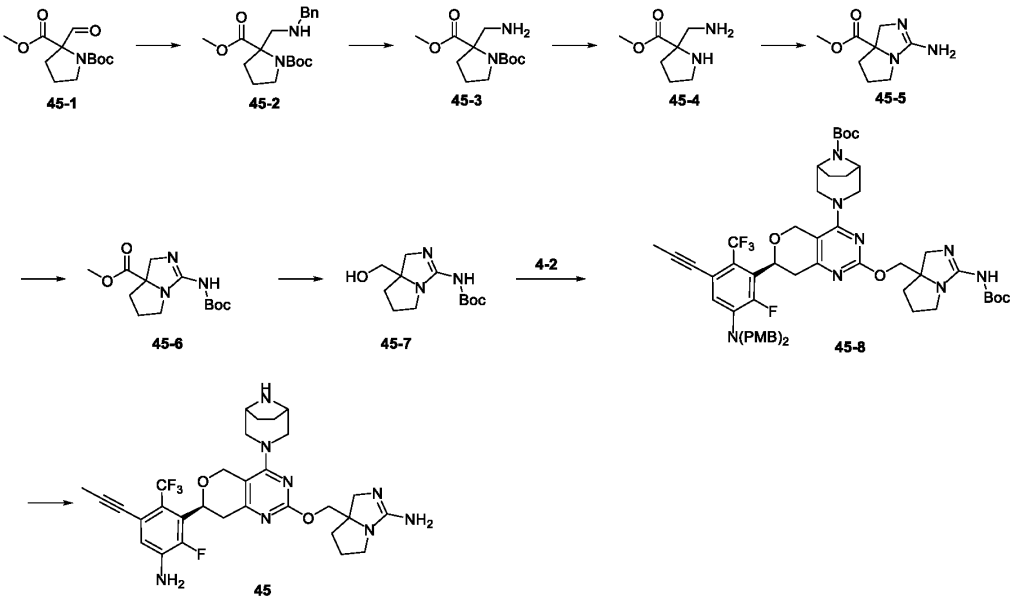
Step 7

To a solution of compound **44-7A** (150 mg, 151.65 μmol) in DCM (5 mL) was added TFA (3 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-55%) to afford compound **44A**. MS m/z = 631.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, J = 8.4 Hz, 1H), 5.63 - 5.34 (m, 1H), 5.30 (d, J = 6.9 Hz, 2H), 5.22 - 5.12 (m, 1H), 4.76 (d, J = 13.7 Hz, 1H), 4.71 (d, J = 13.7 Hz, 1H), 4.58 – 4.50 (m, 2H), 4.34 (d, J = 13.8 Hz, 1H), 4.12 (dd, J = 45.8, 14.6 Hz, 2H), 3.92 (t, J = 12.8 Hz, 2H), 3.78 – 3.51 (m, 3H), 3.30 – 3.15 (m, 3H), 3.08 – 2.99 (m, 1H), 2.91 (d, J = 20.9 Hz, 1H), 2.78 (d, J = 16.0 Hz, 1H), 2.44 – 2.07 (m, 6H), 2.02 (s, 3H).

To a solution of compound **44-7B** (80 mg, 80.88 μmol) in DCM (2 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-75%) to afford compound **44B** as FA salt. MS m/z = 631.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.37 (s, 2H), 6.91 (d, J = 8.5 Hz, 1H), 5.40 - 5.18 (m, 3H), 5.17 - 5.12 (m, 1H), 4.91 (d, J = 13.6 Hz, 1H), 4.73 - 4.55 (m, 1H), 4.53 - 4.45 (m, 2H), 4.33 (d, J = 14.3 Hz, 1H), 4.17 - 3.48 (m, 7H), 3.28 - 3.11 (m, 3H), 3.06 - 2.97 (m,

1H), 2.93 - 2.84 (m, 1H), 2.77 (d, J = 16.0 Hz, 1H), 2.55 - 2.30 (m, 2H), 2.25 - 2.06 (m, 3H), 2.03 - 1.81 (m, 4H).

Example 45



Step 1

To a stirred solution of compound **45-1** (2 g, 7.77 mmol) in MeOH (20 mL) was added benzylamine (832.96 mg, 7.77 mmol), sodium cyanoborohydride (977 mg, 15.55 mmol) and acetic acid (46.68 mg, 0.78 mmol). The resulting mixture was stirred at 25 °C for 16 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 40:1) to afford compound **45-2**. MS m/z = 349.0 $[M+H]^+$.

Step 2

To a stirred solution of compound **45-2** (1.78 g, 5.11 mmol) in MeOH (20 mL) was added Pd/C (1.5 g, 10% purity) and the mixture was stirred at 20 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was concentrated under reduced pressure to afford compound **45-3**. MS m/z = 259.0 $[M+H]^+$.

Step 3

A solution of compound **45-3** (1 g, 3.87 mmol) in HCl (10 mL, 4 M in EtOAc) was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure to afford compound **45-4**. MS m/z = 159.0 $[M+H]^+$.

Step 4

To a stirred solution of compound **45-4** (600 mg, 3.79 mmol) in MeOH (10 mL) was added cyanogen bromide (803.46 mg, 7.59 mmol) and potassium carbonate (1.05 g, 7.59 mmol). The mixture was stirred at 50 °C for 16 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **45-5**. MS m/z = 184.1 $[M+H]^+$.

Step 5

To a stirred solution of compound **45-5** (600 mg, 3.27 mmol) in DCM (10 mL) was added di-tert-butyl dicarbonate (2.86 g, 13.10 mmol), triethyl amine (662.79 mg, 6.55 mmol) and 4-dimethylaminopyridine (200.05 mg, 1.64 mmol). The reaction was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 40:1) to afford compound **45-6**. MS m/z = 284.1 $[M+H]^+$.

Step 6

To a stirred solution of compound **45-6** (270 mg, 0.95 mmol) in MeOH (3 mL) was added sodium methoxide (17.16 mg, 95.3 μmol, 30% in MeOH) and sodium borohydride (33.33 mg, 0.83 mmol) at 0 °C. The mixture was stirred at 25 °C for 8 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **45-7**. MS m/z = 256.1 $[M+H]^+$.

Step 7

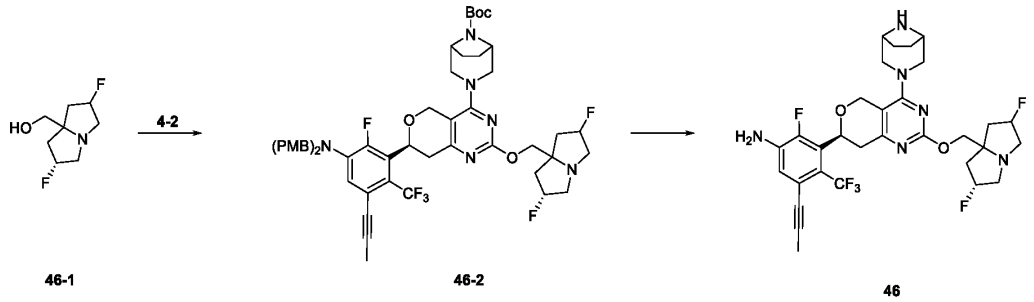
To a stirred solution of compound **45-7** (100 mg, 0.39 mmol) in dry THF (3 mL) was added sodium hydride (31.33 mg, 0.78 mmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (344.66 mg, 0.39 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **45-8**. MS m/z = 1055.5 $[M+H]^+$.

Step 8

The mixture of compound **45-8** (100 mg, 0.94 mmol) in TFA (4 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge C18 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-80%) to afford compound **45**. MS m/z = 615.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.00 (d, *J* = 8.0 Hz, 1H), 5.24 - 5.21 (m, 1H), 5.00 - 4.96 (m, 2H), 4.84 (s, 1H), 4.63 - 4.58 (m,

2H), 4.28-4.21 (m, 2H), 4.11 - 3.92 (m, 3H), 3.75 - 3.72 (m, 1H), 3.66 - 3.56 (m, 2H), 3.49 - 3.35 (m, 2H), 3.05 - 3.00 (m, 1H), 2.26 - 2.15 (m, 6H), 2.02 (m, 5H).

Example 46



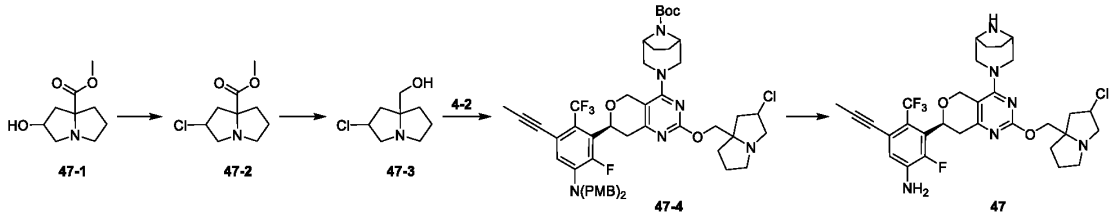
Step 1

To a stirred solution of compound **46-1** (50 mg, 0.28 mmol) in dry THF (5 mL) was added sodium hydride (20 mg, 0.84 mmol, 60% purity) and the mixture was stirred at 25 °C for 0.5 hours under nitrogen atmosphere. Then the solution of compound **4-2** (243 mg, 0.28 mmol) in dry THF (1 mL) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was diluted wtih EtOAc (10 mL), washed with brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **46-2**. MS m/z = 977.7 $[M+H]^+$.

Step 2

The mixture of compound **46-2** (50 mg, 51.00 μmol) in TFA (1 mL) and DCM (3 mL) was stirred at 25 °C for 2 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%HCl); Gradient: (ACN): 55%-70%) to afford compound **46** as HCl salt. MS m/z = 637.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.93 (d, J = 8.0 Hz, 1H), 5.40 - 5.35 (m, 1H), 5.28 - 5.25 (m, 1H), 5.20 - 5.14 (m, 1H), 4.82 - 4.79 (m, 1H), 4.71 - 4.65 (m, 1H), 4.30 (d, J = 8.0 Hz, 1H), 4.27 - 4.18 (m, 2H), 3.98 - 3.79 (m, 2H), 3.64 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 12.0 Hz, 1H), 3.52 - 3.41 (m, 2H), 3.26-3.24 (m, 1H), 3.23 - 3.08 (m, 3H), 2.91-2.83 (m, 1H), 2.52 - 2.43 (m, 1H), 2.35 - 2.32 (m, 1H), 2.26 - 2.12 (m, 3H), 2.04 (s, 3H), 1.97 - 1.94 (m, 1H), 1.88 - 1.79 (m, 1H), 1.65 - 1.59 (m, 1H).

Example 47



Step 1

A solution of compound **47-1** (150 mg, 809.85 μmol) in thionyl chloride (5 mL) was stirred at 80 °C for 2 hours. The reaction was concentrated under reduced pressure to afford crude compound **47-2**. MS m/z = 204.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **47-2** (40 mg, crude) in dry MeOH (3 mL) was added sodium methoxide (7.49 mg, 41.62 μmol, 30% in MeOH) and sodium borohydride (22.29 mg, 392.8 μmol) at 0 °C. The mixture was stirred at 25 °C for 8 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **47-3**. MS m/z = 176.1 $[M+H]^+$.

Step 3

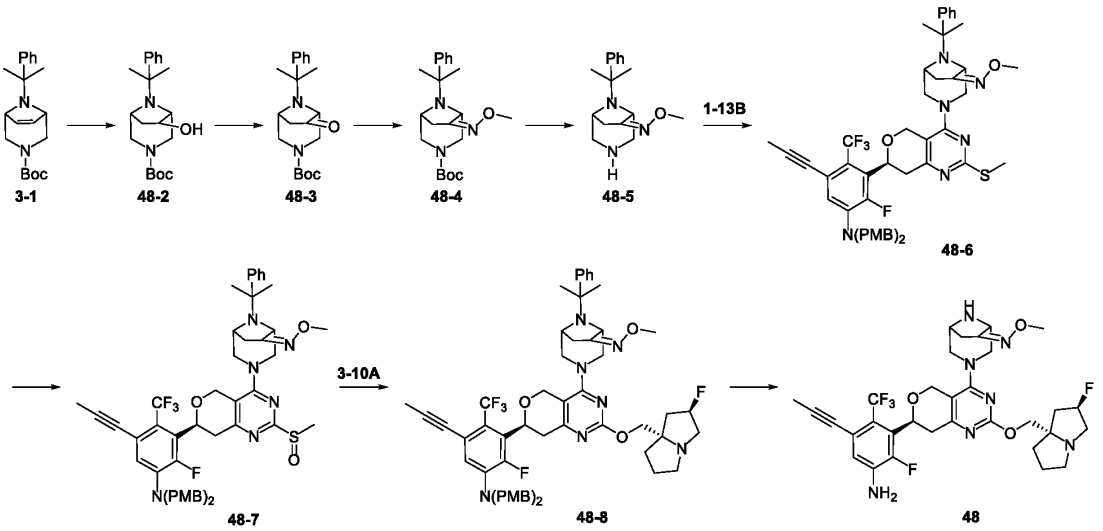
To a stirred solution of compound **47-3** (19.96 mg， 113.64 μmol) in dry THF (3 mL) was added sodium hydride (4.55 mg, 113.64 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (50 mg, 56.82 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **47-4**. MS m/z = 975.7 $[M+H]^+$.

Step 4

The mixture of compound **47-4** (40 mg, 41.00 μmol) in TFA (4 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-70%) to afford compound **47**. MS m/z = 635.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.62 - 4.55 (m, 2H), 4.15 (d, *J* = 16.0 Hz, 1H), 4.11 - 4.02 (m, 2H), 3.65 (s, 2H), 3.58 - 3.43 (m, 3H), 3.26 - 3.19 (m, 1H), 3.10 - 2.98 (m, 3H), 2.91 - 2.83 (m, 2H), 2.67

- 2.62 (m, 1H), 2.07 - 1.94 (m, 8H), 1.93 - 1.85 (m, 3H).

Example 48



Step 1

To a stirred solution of compound **3-1** (500 mg, 1.52 mmol) in THF (10 mL) was added boron trifluoride diethyl etherate (6.08 mL, 6.08 mmol, 1 M) at 0 °C and the mixture was stirred at 25 °C for 8 hours. The reaction was quenched with 5% sodium hydroxide (5 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 hour, then extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **48-2**. MS m/z = 347.3 $[M+H]^+$.

Step 2

To a stirred solution of **48-2** (220 mg, 634.99 μmol) in DCM (10 mL) was added Dess-Martin periodinane (404 mg, 952.48 μmol) at 0 °C and the mixture was stirred at 0 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **48-3**. MS m/z = 345.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **48-3** (100 mg, 290.32 μmol) in dry MeOH (2 mL) was added methoxyamine hydrochloride (29.1 mg, 348.38 μmol) and pyridine (34.5 mg, 435.48 μmol). The mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was redissolved in DCM (10 mL), washed with 2 M HCl (10 mL) and brine (10 mL), dried

over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **48-4**. MS m/z = 374.4 $[M+H]^+$.

Step 4

A solution of compound **48-4** (80 mg, 214.20 μmol) in HCl (2 mL, 4 M in EtOAc) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure to afford compound **48-5**. MS m/z = 274.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **48-5** (50 mg, 182.90 μmol) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (118.2 mg, 914.50 μmol) and **1-13B** (143.7 mg, 182.90 μmol). The resulting mixture was stirred at 100 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **48-6**. MS m/z = 909.6 $[M+H]^+$.

Step 6

To a stirred solution of compound **48-6** (135 mg, 148.51μmol) in dry THF (2 mL) was added 3-chloroperoxybenzoic acid (33.2 mg, 163.36 μmol) and the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure to afford crude compound **48-7**. MS m/z = 925.5 $[M+H]^+$.

Step 7

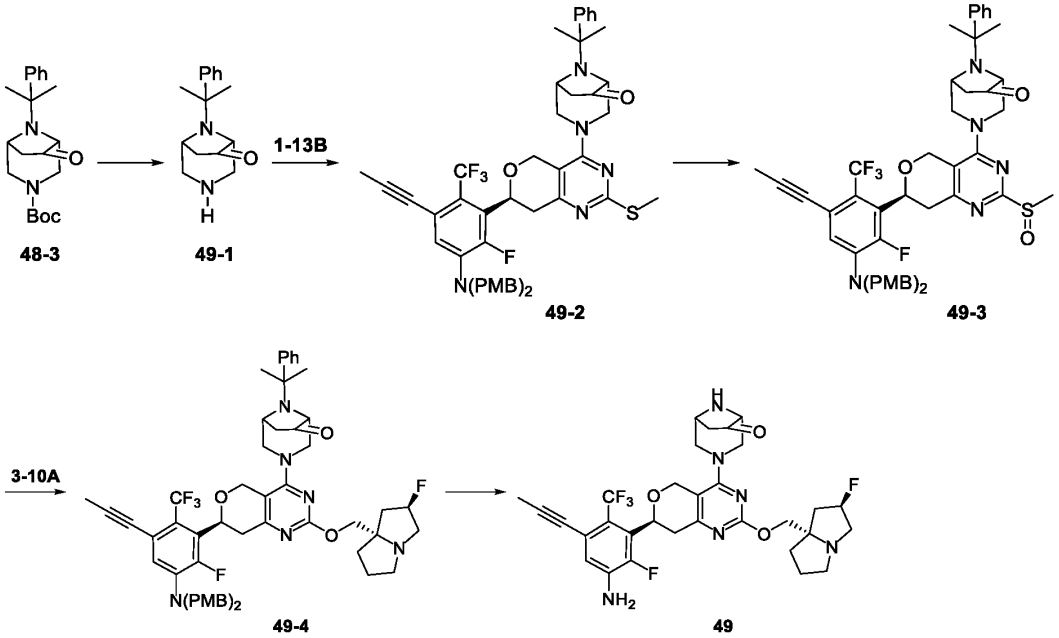
To a stirred solution of compound **3-10A** (25.6 mg, 160.53 μmol) in dry THF (2 mL) was added sodium hydride (6.4 mg, 160.53 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 1 hour. Then compound **48-7** (135 mg, crude) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **48-8**. MS m/z = 1020.8 $[M+H]^+$.

Step 8

The mixture of compound **48-8** (60 mg, 58.82 μmol) in TFA (0.5 mL) and DCM (1.5 mL) was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18 150*40mm, 5μm, ACN-H_2O (0.05%FA); Gradient: (ACN): 10%-50%) to afford compound **48** as FA salt. MS m/z = 662.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.44 (s, 0.41H), 6.91 (d, J = 8.0 Hz, 1H), 5.47 (d, J = 52.0 Hz, 1H), 5.16 - 5.11 (m, 1H), 4.77 - 4.72 (m, 1H), 4.66 - 4.55 (m, 1H), 4.40 (dd, J = 12.0 Hz, 4.0 Hz, 1H),

4.31 (d, J = 12.0 Hz, 1H), 4.14 - 4.00 (m, 1H), 3.88 - 3.77 (m, 4H), 3.76 - 3.63 (m, 5H), 3.55 - 3.42 (m, 1H), 3.27 - 3.04 (m, 3H), 2.87 (dd, J = 20.0 Hz, 4.0 Hz, 1H), 2.72 - 2.54 (m, 2H), 2.49 - 2.38 (m, 2H), 2.29 - 2.16 (m, 3H), 2.09 - 2.01 (m, 4H).

Example 49



Step 1

To a stirred solution of compound **48-3** (60 mg, 174.19 μmol) in DCM (5 mL) was added HCl (5 mL, 4 M in EtOAc) and the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford compound **49-1**. MS m/z = 245.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **49-1** (40 mg, 163.71 μmol) in N,N-dimethylformamide (5 mL) was added N,N-diisopropylethylamine (105.8 mg, 818.56 μmol) and **1-13B** (128.6 mg, 163.71 μmol). The resulting mixture was stirred at 80 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **49-2**. MS m/z = 880.7 $[M+H]^+$.

Step 3

To a stirred solution of compound **49-2** (120 mg, 136.36 μmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (47.1 mg, 272.73 μmol) and the mixture was stirred at 25 °C for 1 hour.

The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **49-3**. MS m/z = 896.3 $[M+H]^+$.

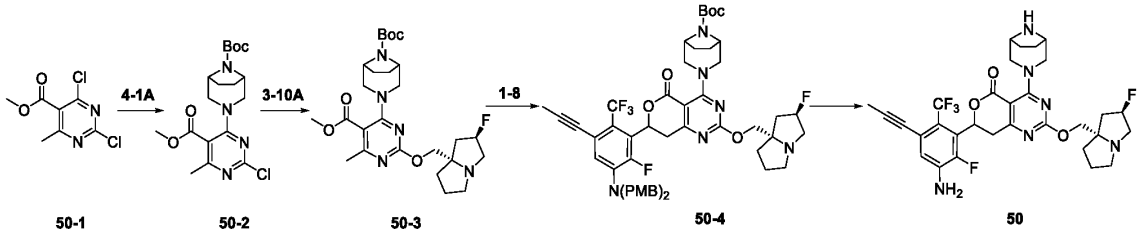
Step 4

To a stirred solution of compound **3-10A** (41.9 mg, 263.16 μmol) in dry THF (3 mL) was added sodium hydride (5.8 mg, 394.74 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **49-3** (120 mg, 133.88 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **49-4**. MS m/z = 991.8 $[M+H]^+$.

Step 5

The mixture of compound **49-4** (120 mg, 121.08 μmol) in TFA (4 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-70%) to afford compound **49**. MS m/z = 633.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.45 (d, *J* = 52.0 Hz, 1H), 5.15 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.80 - 4.75 (m, 2H), 4.58 (dd, *J* = 32.0 Hz, 16.0 Hz, 1H), 4.42 - 4.35 (m, 1H), 4.30 - 4.25 (m, 1H), 4.23 - 4.00 (m, 1H), 3.95 - 3.92 (m, 1H), 3.84 - 3.56 (m, 5H), 3.48 - 3.33 (m, 2H), 3.28 - 3.10 (m, 3H), 2.90 - 2.84 (m, 1H), 2.55 - 2.38 (m, 3H), 2.28 - 2.15 (m, 3H), 2.01 (s, 3H).

Example 50



Step 1

To a stirred solution of compound **50-1** (1.8 g, 8.14 mmol) in ethanol (30 mL) was added N,N-diisopropylethylamine (2.1 g, 16.29 mmol, 2.84 mL) and compound **4-1A** (1.82 g, 8.55 mmol). The resulting mixture was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4.

After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:EtOAc = 10:1) to afford compound **50-2**. MS m/z = 397.1 $[M+H]^+$.

Step 2

To a stirred solution of compound 3-10A (72.21 mg, 453.55 μmol) and compound **50-2** (100 mg, 251.97 μmol) in dry THF (3 mL) was added sodium hydride (29.02 mg, 1.21 mmol, 60% purity) at 0 °C. The mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (2 mL), extracted wtih EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:2) to afford compound **50-3**. MS m/z = 520.5 $[M+H]^+$.

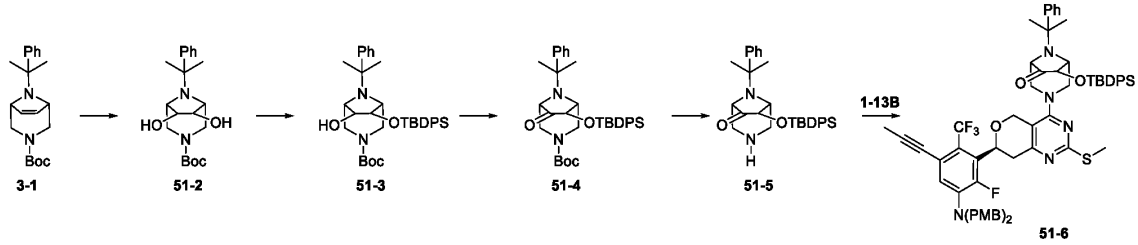
Step 3

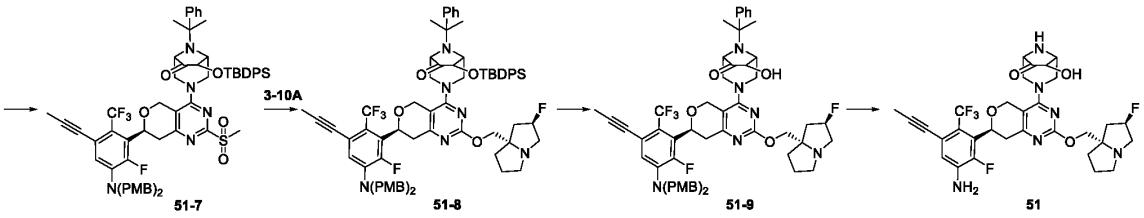
To a stirred solution of compound **50-3** (100 mg, 192.45 μmol) in dry THF (3 mL) was added lithium diisopropylamide (24.74 mg, 230.94 μmol, 2.0 M in THF) at -78 °C and the mixture was stirred at -78 °C for 40 minutes. Then the solution of compound **1-8** (93.37 mg, 192.45 μmol) in dry THF (1 mL) was added slowly at -78 °C, and the reaction was stirred at 0 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **50-4**. MS m/z = 973.7 $[M+H]^+$.

Step 4

The mixture of compound **50-4** (85 mg, 87.36 μmol) in TFA (1 mL) and DCM (3 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 40%-75%) to afford compound **50** as FA salt. MS m/z = 633.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.48 (s, 0.50 H), 6.98 (d, J = 8.4 Hz, 1H), 5.99 (d, J = 12.8 Hz, 1H), 5.39 (d, J = 52.0 Hz, 1H), 4.98 - 4.95 (m, 1H), 4.39 - 4.26 (m, 2H), 4.08 (s, 1H), 3.96 (s, 1H), 3.76 - 3.72 (m, 1H), 3.63 - 3.53 (m, 2H), 3.49 - 3.34 (m, 4H), 3.18 - 3.12 (m, 1H), 3.02 (dd, J = 20.0 Hz, 4.0 Hz, 1H), 2.42 - 2.18 (m, 4H), 2.11 - 2.06 (m, 2H), 2.02 - 1.94 (m, 6H), 1.86 - 1.78 (m, 1H).

Example 51





Step 1

To a stirred solution of compound **3-1** (1 g, 3.04 mmol) in acetonitrile (10 mL) and water (2 mL)was added potassium dioxidodioxoosmium dihydrate (26.70 mg, 91.34 μmol) and 4-methylmorpholine N-oxide (713.36 mg, 6.09 mmol). The mixture was stirred at 25 °C for 16 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **51-2**. MS m/z = 363.4 $[M+H]^+$.

Step 2

To a stirred solution of compound **51-2** (600 mg, 1.66 mmol) in DCM (10 mL) was added imidazole (338.07 mg, 4.97 mmol) tert-butylchlorodiphenylsilane (545.99 mg, 1.99 mmol). The reaction was stirred at 25 °C for 3 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **51-3**. MS m/z = 601.6 $[M+H]^+$.

Step 3

To a stirred solution of compound **51-3** (300 mg, 499.28 μmol) in DCM (10 mL) was added Dess-Martin periodinane (317.65 mg, 748.93 μmol) at 0 °C. The reaction was stirred at 25 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **51-4**. MS m/z = 599.5 $[M+H]^+$.

Step 4

To a stirred solution of compound **51-4** (100 mg, 166.99 μmol) in DCM (10 mL) was added zinc bromide (45.13 mg，200.39 μmol) at 25 °C and the mixture was stirred at 25 °C for 2 hours. The reaction was filtered, the filter was washed with DCM (3 × 20 mL), the filtrate was concentrated under reduced pressure to afford compound **51-5**. MS m/z = 499.5 $[M+H]^+$.

Step 5

To a stirred solution of compound **51-5** (80 mg, 160.41 μmol) in dry N,N-dimethylformamide (5 mL) was added N,N-diisopropylethylamine (103.66 mg, 802.04 μmol) and **1-13B** (126.04 mg, 160.41 μmol). The resulting mixture was stirred at 80 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **51-6**. MS m/z = 1134.8 $[M+H]^+$.

Step 6

To a stirred solution of compound **51-6** (120 mg, 105.78 μmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (53.69 mg, 264.46 μmol) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **51-7**. MS m/z = 1166.8 $[M+H]^+$.

Step 7

To a stirred solution of compound **3-10A** (40.95 mg, 257.20 μmol) in dry THF (3 mL) was added sodium hydride (10.29 mg, 257.20 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **51-7** (120 mg, 102.88 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **51-8**. MS m/z =1246.0 $[M+H]^+$.

Step 8

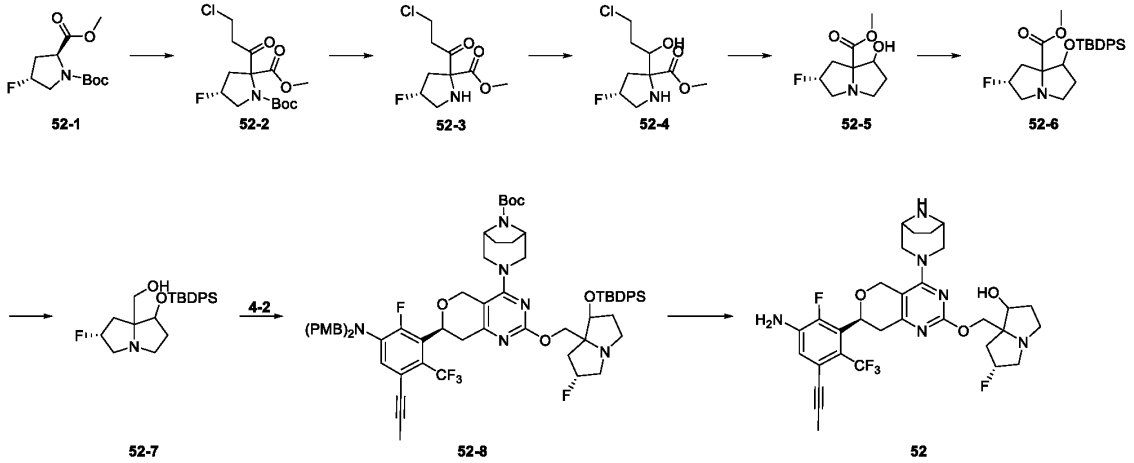
To a stirred solution of compound **51-8** (85 mg, 68.25 μmol) in dry THF (5 mL) was added tetrabutylammonium fluoride (0.34 mL, 341.23 μmol, 1 M in THF) at 25 °C and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **51-9**. MS m/z = 1007.8 $[M+H]^+$.

Step 9

The mixture of compound **51-9** (80 mg, 79.44 μmol) in TFA (4 mL) was stirred at 25 °C for 1

hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-70%) to afford compound **51**. MS m/z = 649.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.96 (d, *J* = 8.0 Hz, 1H), 5.60 (d, *J* = 52.0 Hz, 1H), 5.42 - 5.30 (m, 1H), 5.23 - 5.13 (m, 1H), 4.96 - 4.90 (m, 2H), 4.28 - 3.82 (m, 7H), 3.75 - 3.60 (m, 1H), 3.48 - 3.38 (m, 2H), 3.13 - 3.07 (m, 1H), 2.86 - 2.70 (m, 1H), 2.67 - 2.53 (m, 2H), 2.34 - 2.23 (m, 4H), 2.06 - 2.02 (m, 5H).

Example 52



Step 1

To a stirred solution of compound **52-1** (500 mg, 2.02 mmol) in dry THF (15 mL) was added lithium bis(trimethylsilyl)amide (2.02 ml, 2.02 mmol, 1 M in THF) at -70 °C and the mixture was stirred at -70 °C for 30 minutes. Then the solution of 3-chloropropionyl chloride (384.81 mg, 3.03 mmol) in dry THF (2 mL) was added at -70 °C, and the reaction was stirred at -70 °C for 15 minutes. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **52-2**. MS m/z = 338.1 $[M+H]^+$.

Step 2

To a solution of compound **52-2** (50 mg, 0.15 mmol) in DCM (3 mL) was added TFA (0.5 mL) at 0 °C, the mixture was stirred at 25 °C for 15 minutes. The reaction was concentrated under reduced pressure to afford compound **52-3**. MS m/z = 238.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **52-3** (50 mg, 0.22 mmol) in MeOH (3 mL) was added sodium borohydride (41.80 mg, 1.10 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction was quenched with 1 N HCl (1 mL), and concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 30:1) to afford compound **52-4**. MS m/z = 240.1 $[M+H]^+$.

Step 4

To a stirred solution of compound **52-4** (100 mg, 0.42 mmol) in acetonitrile (4 mL) was added potassium carbonate (115.92 mg, 0.84 mmol) and the mixture was stirred at 60 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **52-5**. MS m/z = 204.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **52-5** (50 mg, 0.25 mmol) in DCM (20 mL) was added tert-butylchlorodiphenylsilane (137.43 mg, 0.50 mmol), imidazole (68 mg, 1.00 mmol) and 4-dimethylaminopyridine (15.86 mg, 0.13 mmol). The reaction was stirred at 40 °C for 16 hours. The reaction was diluted with water (10 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 30:1) to afford compound **52-6**. MS m/z = 442.2 $[M+H]^+$.

Step 6

To a stirred solution of compound **52-6** (50 mg, 0.11 mmol) in dry THF (3 mL) was added lithium aluminum hydride (0.10 ml, 0.22 mmol, 2.5 M in THF) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 15 minutes. The reaction was quenched with water (0.2 mL) and 15% NaOH solution (0.2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes. The reaction was filtered, the filter was washed with THF (5 mL), the filtrate was concentrated under reduced pressure to afford compound **52-7**. MS m/z = 414.2 $[M+H]^+$.

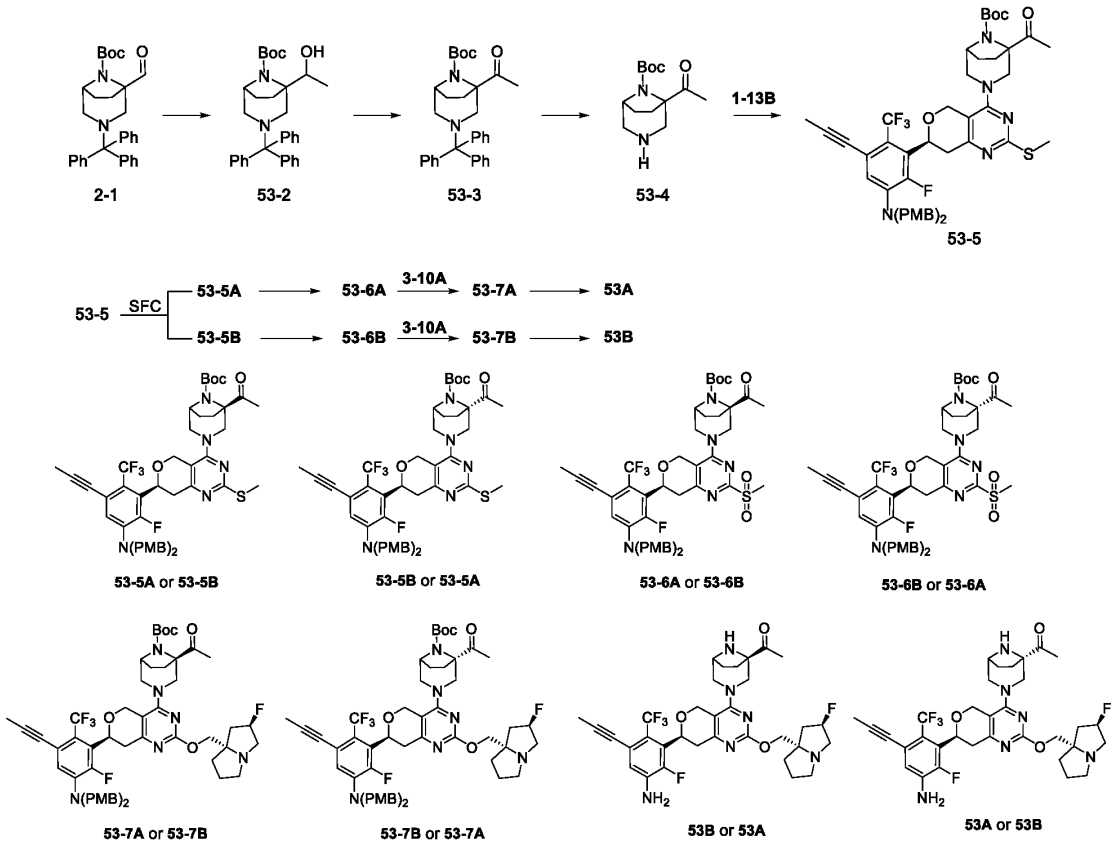
Step 7

To a stirred solution of compound **52-7** (90 mg, 0.22 mmol) in dry THF (5 mL) was added sodium hydride (15.91 mg, 0.66 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **4-2** (195.41 mg, 0.22 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **52-8**. MS m/z = 1213.5 $[M+H]^+$.

Step 8

The mixture of compound **52-8** (60 mg, 0.05 mmol) in TFA (1 mL) and DCM (2 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 10%-40%) to afford compound **52** as FA salt. MS m/z = 635.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.39 (s, 0.91H), 6.91 (d, J = 8.0 Hz, 1H), 5.47 - 5.27 (m, 1H), 5.22 - 5.14 (m, 1H), 4.75 - 4.50 (m, 2H), 4.44 - 4.39 (m, 1H), 4.31 - 4.20 (m, 2H), 4.10 (d, J = 8.0 Hz, 2H), 3.92 - 3.76 (m, 2H), 3.65 - 3.58 (m, 2H), 3.45 - 3.35 (m, 1H), 3.30 - 3.15 (m, 3H), 3.02 - 2.88 (m, 2H), 2.61 (t, J = 16.0 Hz, 1H), 2.34 - 2.03 (m, 5H), 2.02 (s, 3H), 2.00 - 1.86 (m, 2H).

Example 53



Step 1

To a stirred solution of compound **2-1** (200 mg, 414.41 μmol) in THF (10 mL) was added methylmagnesium bromide (186 μL, 1.86 mmol, 1 M in THF) at -60 °C under nitrogen atmosphere and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **53-2**. MS m/z = 499.4 $[M+H]^+$.

Step 2

To a stirred solution of compound **53-2** (230 mg, 461.24 μmol) in DCM (10 mL) was added Dess-Martin periodinane (391.26 mg, 922.48 μmol) at 0 °C. The reaction was stirred at 0 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **53-3**. MS m/z = 497.4 $[M+H]^+$.

Step 3

To a stirred solution of compound **53-3** (100 mg, 201.35 μmol) in DCM (5 mL) was added HCl (5 mL, 4 M in EtOAc) and the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford compound **53-4**. MS m/z = 255.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **53-4** (50 mg, 196.60 μmol) in N,N-dimethylformamide (5 mL) was added N,N-diisopropylethylamine (127.04 mg, 983.00 μmol) and **1-13B** (185.37 mg, 235.92 μmol). The resulting mixture was stirred at 80 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **53-5**. The compound **53-5** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®IG-10, 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: EtOH +(0.05%)(NH_3 in MeOH); Gradient: B% 40%) to afford compound **53-5A** and compound **53-5B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®IG-10, 4.6*150mm, 5μm; Mobile phase: A: Supercritical CO_2; B: (EtOH (0.05% - DEA); Gradient: B% 40%). Compound **53-5A**, Rt = 3.202 mins, MS m/z = 890.8 $[M+H]^+$; compound **53-5B**, Rt = 7.309 mins, MS m/z = 890.8 $[M+H]^+$.

Step 5

To a stirred solution of compound **53-5A** (40 mg, 44.94 μmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (19.39 mg, 112.36 μmol) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by

flash chromatography (PE:EtOAc = 1:1) to afford compound **53-6A**. MS m/z = 922.7 $[M+H]^+$.

Step 6

To a stirred solution of compound **3-10A** (17.27 mg, 108.46 μmol) in dry THF (3 mL) was added sodium hydride (4.34 mg, 108.46 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **53-6A** (40 mg, 43.38 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **53-7A**. MS m/z = 1001.8 $[M+H]^+$.

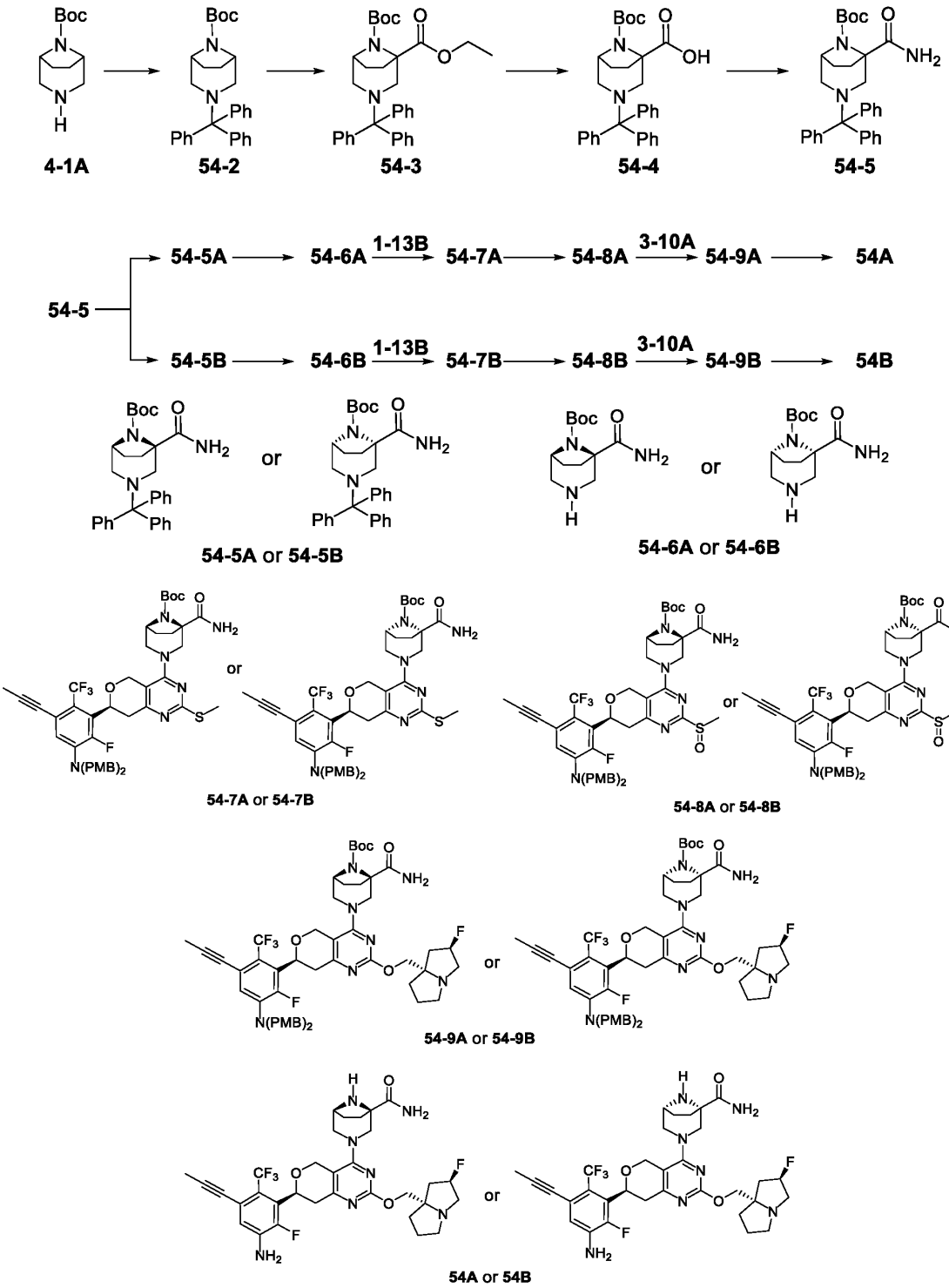
Step 7

The mixture of compound **53-7A** (20 mg, 19.98 μmol) in TFA (4 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 55%-70%) to afford compound **53A** as FA salt. MS m/z = 661.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.31 (s, 1.56H), 6.92 (d, J = 8.0 Hz, 1H), 5.55 (d, J = 52.0 Hz, 1H), 5.20 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.81 - 4.70 (m, 2H), 4.52 - 4.48 (m, 2H), 3.97 - 3.77 (m, 4H), 3.68 - 3.51 (m, 2H), 3.45 - 3.32 (m, 2H), 3.29 - 3.24 (m, 1H), 3.11 - 3.08 (m, 1H), 2.92 (dd, J = 20.0 Hz, 4.0 Hz, 1H), 2.72 - 2.66 (m, 1H), 2.59 - 2.44 (m, 2H), 2.38 (s, 3H), 2.34 - 2.28 (m, 2H), 2.21 - 2.07 (m, 3H), 2.02 (s, 3H), 1.96 - 1.78 (m, 2H).

Step 8

With reference to steps 5~7, compound **53-5A** was replaced with compound **53-5B** as the raw material to obtain compound **53B** as FA salt. MS m/z = 661.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.16 (s, 0.87H), 6.92 (d, J = 8.0 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 5.24 - 5.20 (m, 1H), 4.81 - 4.73 (m, 2H), 4.58 - 4.51 (m, 2H), 4.15 - 3.96 (m, 3H), 3.91 - 3.68 (m, 4H), 3.53 - 3.41 (m, 2H), 3.27 - 3.17 (m, 1H), 2.97 - 2.92 (m, 1H), 2.74 - 2.69 (m, 1H), 2.63 - 2.51 (m, 2H), 2.39 - 2.29 (m, 6H), 2.25 - 2.17 (m, 3H), 2.14 - 2.04 (m, 1H), 2.02 (s, 3H).

Example 54



Step 1

To a stirred solution of compound **4-1A** (5 g, 23.55 mmol) in acetonitrile (50 mL) was added triethylamine (9.53 g, 94.21 mmol) and trityl chloride (7.22 g, 25.91 mmol). The mixture was stirred

at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **54-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49-7.47 (m, 6H), 7.27-7.23 (m, 6H), 7.15-7.12 (m, 3H), 4.15 (s, 1H), 4.02 (s, 1H), 2.96 (d, *J* = 8.0 Hz, 2H), 2.38-2.33 (m, 2H), 2.00-1.97 (m, 2H), 1.83-1.72 (m, 2H), 1.25 (s, 9H).

Step 2

To a stirred solution of compound **54-2** (200 mg, 0.44 mmol) in dry diethyl ether (5 mL) was added N,N,N',N'-tetramethylethylenediamine (77 mg, 0.66 mmol) at -40 °C and stirred at -40 °C for 5 minutes. Then sec-butyllithium (0.858 mL, 0.66 mmol, 1.3 M in hexae) was added at -40 °C and the resulting mixture was stirred at -40 °C for 30 minutes. After that, ethyl chloroformate (96 mg, 0.88 mmol) was added slowly at -70 °C, and the reaction was stirred at -70 °C for 30 minutes. The reaction was quenched with saturated NH_4Cl solution (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **54-3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48-7.46 (m, 6H), 7.27-7.23 (m, 6H), 7.15-7.11 (m, 3H), 4.20 (d, *J* = 4.0 Hz,1H), 4.12 (q, *J* = 8.0 Hz, 2H), 3.36 (d, *J* = 12.0 Hz, 1H), 2.92 (d, *J* = 12.0 Hz, 1H), 2.86-2.79 (m, 1H), 2.69-2.63 (m, 1H), 2.23-2.08 (m, 2H), 2.02 (d, *J* = 12.0 Hz, 1H), 1.86 (d, *J* = 12.0 Hz, 1H), 1.25 (t, *J* = 8.0 Hz, 3H), 1.15 (s, 9H).

Step 3

To a stirred solution of compound **54-3** (240 mg, 0.46 mmol) in ethanol (2 mL) and water (1 mL) was added potassium hydroxide (128 mg, 2.30 mmol). The mixture was stirred at 110 °C for 16 hours. The reaction was quenched with diluted HCl (2 mL, 1 M), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **54-4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.44 (s, 1H), 7.41-7.29 (m, 12H), 7.18-7.14 (m, 3H), 3.20 (d, *J* = 12.0 Hz, 1H), 2.79 (d, *J* = 12.0 Hz, 1H), 2.62-2.57 (m, 1H), 2.28-2.23 (m, 1H), 2.19-2.13 (m, 1H), 2.10-1.96 (m, 1H), 2.00 (m, 1H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.62 (d, *J* = 8.0 Hz, 1H), 1.05 (s, 9H).

Step 4

To a stirred solution of compound **54-4** (120 mg, 0.24 mmol) in N,N-dimethylformamide (2 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70 mg, 0.36 mmol) and 1-hydroxybenzotriazole (55 mg, 0.36 mmol). The resulting mixture was stirred at 25 °C for 10 minutes. Then ammonium hydroxide (0.25 mL, 0.24 mmol) was added and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (2 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure to afford compound **54-5**. MS m/z = 498.4 $[M+H]^+$. The compound **54-5** was separated by preparative SFC (Column name:

DAICEL CHIRALPAK®AS-10, 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: EtOH +(0.05%)(NH_3 in MeOH); Gradient: B% 80%-20%) to afford compound **54-5A** and compound **54-5B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®AS-10, 4.6*150mm, 5μm; Mobile phase: A: Supercritical CO_2; B: (EtOH (0.05% - DEA); Gradient: B% 5%-40%, 4 min). Compound **54-5A**, Rt = 2.824 min mins, ee: 97.05%, MS m/z = 498.4 $[M+H]^+$; compound **54-5B**, Rt = 3.327 mins, ee: 96.10%, MS m/z = 498.4 $[M+H]^+$.

Step 5

To a stirred solution of compound **54-5A** (0.036 g, 72.34 μmol) in 1,4-dioxane (2 mL) was added diluted HCl (0.5 mL, 1 M) and the mixture was stirred at 25 °C for 12 hours. The reaction was concentrated under reduced pressure to afford compound **54-6A**, MS m/z = 256.3 $[M+H]^+$.

With reference to step 5, compound **54-5A** was replaced with compound **54-5B** as the raw material to obtain compound **54-6B**. MS m/z =256.3 $[M+H]^+$.

Step 6

To a stirred solution of compound **54-6A** (20 mg, 78.34 μmol) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (30.37 mg, 235.01 μmol) and **1-13B** (73.86 mg, 94.00 μmol). The resulting mixture was stirred at 100 °C for 1 hour. The reaction was quenched with water (2 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **54-7A**. MS m/z = 891.3 $[M+H]^+$.

With reference to step 6, compound **54-6A** was replaced with compound **54-6B** as the raw material to obtain compound **54-7B**. MS m/z = 891.3 $[M+H]^+$.

Step 7

To a stirred solution of compound **54-7A** (45 mg, 50.51 μmol) in THF (2 mL) was added 3-chloroperoxybenzoic acid (8.72 mg, 50.51 μmol, 85% purity) and the mixture was stirred at 20 °C for 2 hours under nitrogen atmosphere. The reaction was quenched with saturated solution of sodium sulfite (2 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 6:1) to afford compound **54-8A**. MS m/z = 907.3 $[M+H]^+$.

With reference to step 7, compound **54-7A** was replaced with compound **54-7B** as the raw material to obtain compound **54-8B**. MS m/z = 907.3 $[M+H]^+$.

Step 8

To a stirred solution of compound **3-10A** (11.85 mg, 74.42 μmol) in dry THF (2 mL) was added sodium hydride (3.57 mg, 148.85 μmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours.

Then compound **54-8A** (45.00 mg, 49.62 μmol) was added and the resulting mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **54-9A**. MS m/z = 1002.8 $[M+H]^+$.

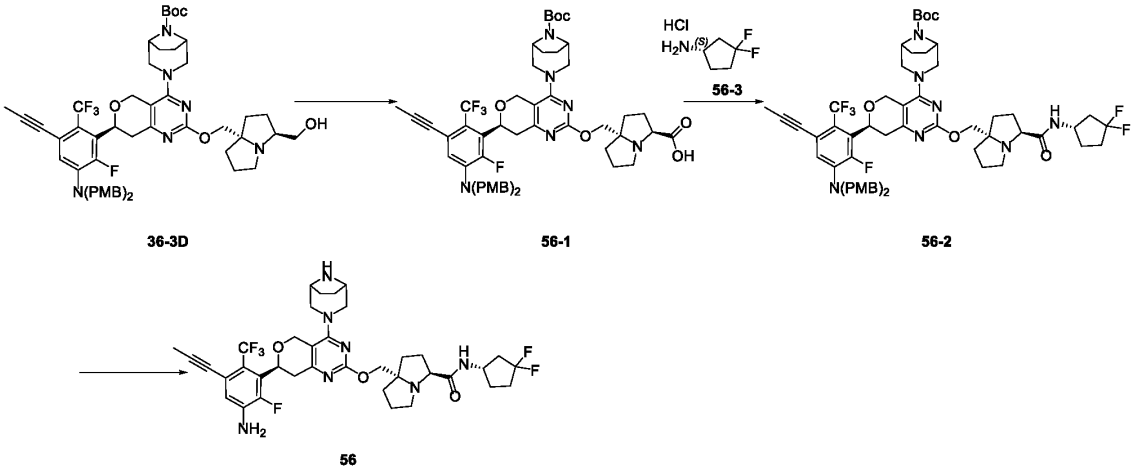
With reference to step 8, compound **54-8A** was replaced with compound **54-8B** as the raw material to obtain compound **54-9B**. MS m/z = 1002.8 $[M+H]^+$.

Step 9

To a solution of compound **54-9A** (48 mg, 47.90 μmol) in DCM (2 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-75%) to afford compound **54A**. MS m/z = 662.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, J = 8.0 Hz, 1H), 5.52 (d, J = 52.0 Hz, 1H), 5.18 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.88 (s, 1H), 4.76-4.69 (m, 2H), 4.50-4.40 (m, 2H), 3.80-3.76 (m, 2H), 3.69 (d, J = 4 Hz, 1H), 3.55-3.52 (m, 1H), 3.42-3.37 (m, 2H), 3.28-3.21 (m, 2H), 2.99 (d, J = 16.0 Hz, 1H), 2.90 (dd, J = 16.0 Hz, 4.0 Hz, 1H), 2.64-2.46 (m, 2H), 2.37-2.35 (m, 1H), 2.37-2.35 (m, 3H), 2.14-2.09 (m, 1H), 2.04-1.98 (m, 4H), 1.88-1.82 (m, 1H), 1.67-1.61 (m, 1H).

To a solution of compound **54-9B** (46 mg, 45.90 μmol) in DCM (2 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 55%-70%) to afford compound **54B** as FA salt. MS m/z = 662.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.38 (s, 0.41H), 6.92 (d, J = 12.0 Hz, 1H), 5.51 (d, J = 52.0 Hz, 1H), 5.19 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.47-4.39 (m, 2H), 4.12 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 12.0 Hz, 1H), 3.87-3.67 (m, 4H), 3.39-3.34 (m, 3H), 3.27-3.23 (m, 1H), 3.02 (d, J = 16.0 Hz, 1H), 2.91 (dd, J = 16.0 Hz, 4.0 Hz, 1H), 2.65-2.44 (m, 2H), 2.36-2.31 (m, 1H), 2.27-2.21 (m, 2H), 2.07-1.98 (m, 7H), 1.91-1.87 (m, 1H).

Example 56



Step 1

To a stirred solution of compound **36-3D** (445 mg, 458.25 μmol) in N,N-dimethylformamide (13 mL) was added pyridinium dichromate (1.38 g, 3.67 mmol) and the resulting mixture was stirred at 25 °C for 24 hours. The reaction was dilued with water (50 mL), extracted wtih EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **56-1**, which was used in the next step directly. MS m/z = 985.7 $[M+H]^+$.

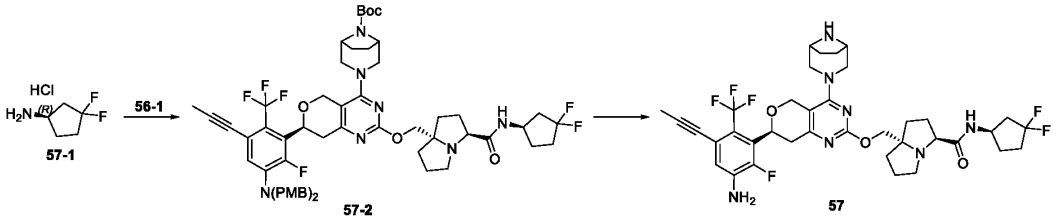
Step 2

To a stirred solution of compound **56-1** (200 mg, crude) in DCM (2.5 mL) was added N,N-diisopropylethylamine (78.72 mg, 609.12 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (154.40 mg, 406.08 μmol) and (S)-3,3-difluorocyclopentanamine hydrochloride (24.59 mg, 203.03 μmol). The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **56-2**. MS m/z = 1088.7 $[M+H]^+$.

Step 3

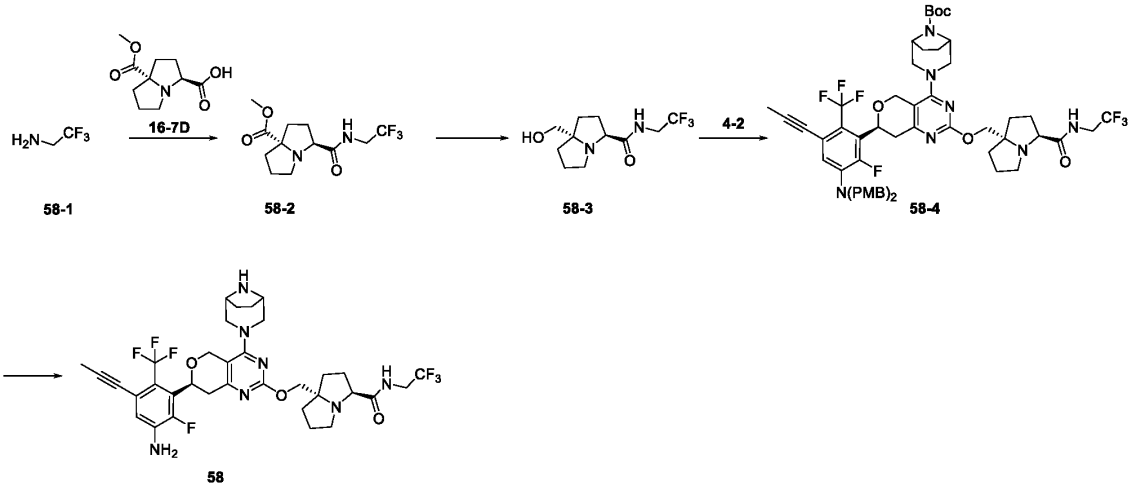
To a solution of compound **56-2** (95 mg, 87.30 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **56**. MS m/z = 748.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, J = 8.0 Hz, 1H), 5.19 - 5.12 (m, 1H), 4.82 - 4.76 (m, 1H), 4.68 - 4.61 (m, 1H), 4.32 (p, J = 8.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.78 - 3.71 (m, 1H), 3.60 - 3.48 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.27 - 3.13 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.95 - 2.80 (m, 2H), 2.80 - 2.68 (m, 1H), 2.57 - 2.41 (m, 1H), 2.30 - 2.03 (m, 6H), 2.01 (s, 3H), 2.00 - 1.78 (m, 8H), 1.79 - 1.64 (m, 3H).

Example 57



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **57-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 49%-69%) to afford compound **57**. MS m/z = 748.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.34 - 4.27 (m, 1H), 4.15 (t, J = 12.0 Hz, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.55 - 3.51 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.91 - 2.82 (m, 2H), 2.75 - 2.69 (m, 1H), 2.55 - 2.43 (m, 1H), 2.29 - 2.08 (m, 5H), 2.06 - 1.96 (m, 6H), 1.94 - 1.82 (m, 6H), 1.78 - 1.67 (m, 3H).

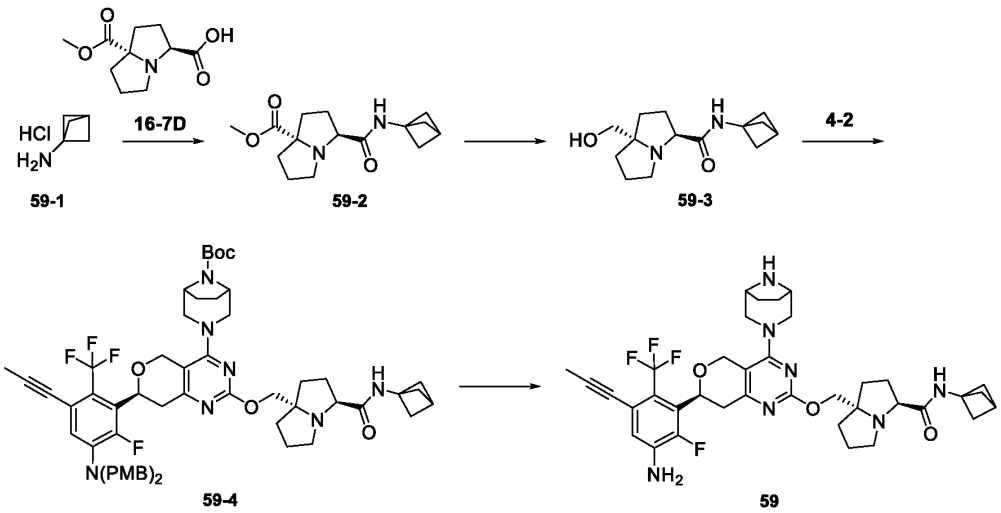
Example 58



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **58-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **58**. MS m/z = 726.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.18 - 5.10 (m, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.08 - 3.96 (m, 2H), 3.92 - 3.78 (m, 2H), 3.57 - 3.48 (m, 3H), 3.45

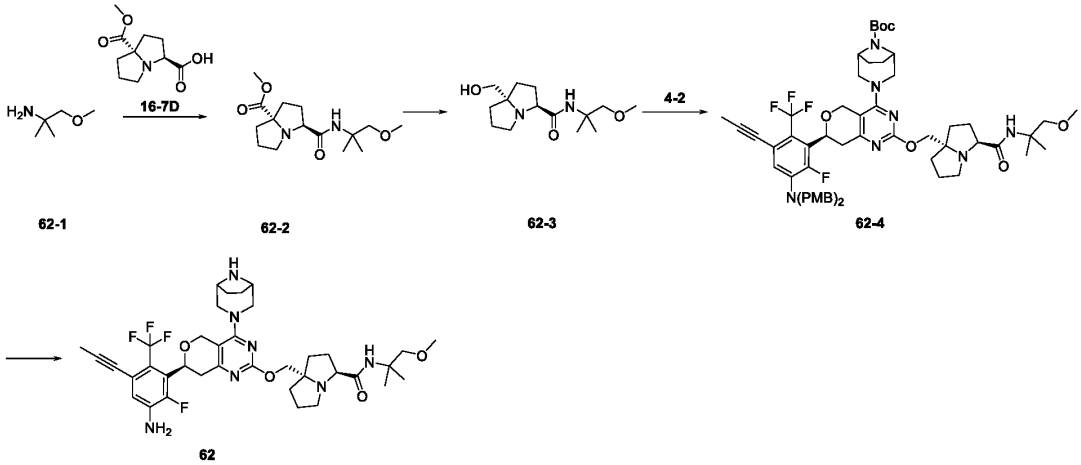
- 3.38 (m, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.75 - 2.67 (m, 1H), 2.15 - 1.97 (m, 7H), 1.97 - 1.78 (m, 6H), 1.77 - 1.64 (m, 2H).

Example 59



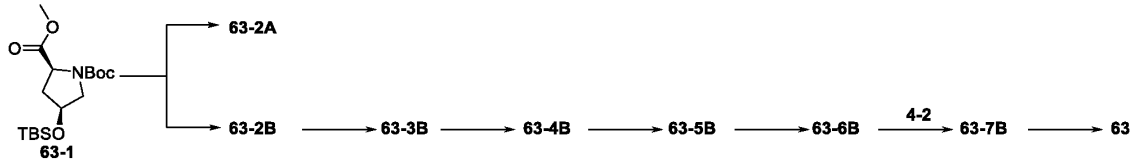
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **59-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **59**. MS m/z = 710.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 - 5.12 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.69 - 3.65 (m, 1H), 3.56 - 3.51 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.78 - 2.72 (m, 1H), 2.11 - 2.05 (m, 8H), 2.04 - 1.98 (m, 5H), 1.96 - 1.82 (m, 7H), 1.75 - 1.67 (m, 2H).

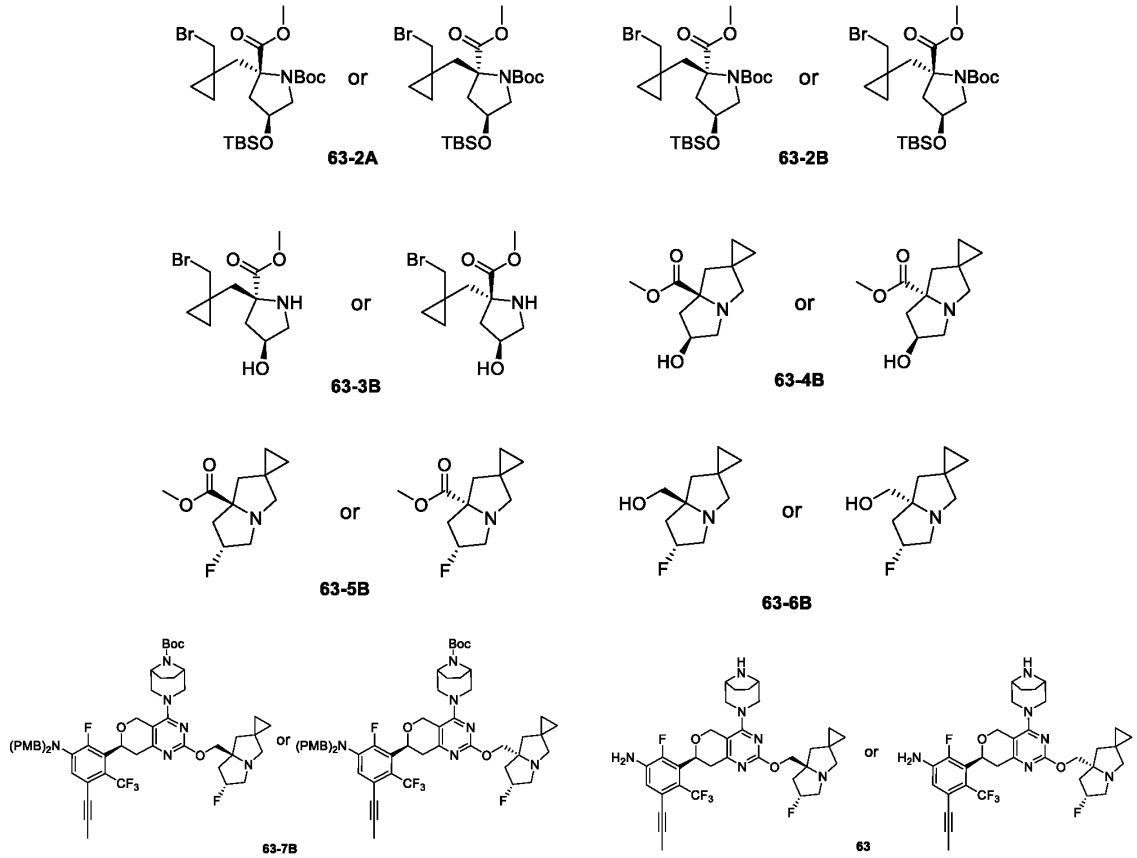
Example 62



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **62-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **62**. MS m/z = 730.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.10 (m, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.21 - 4.09 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.68 (m, 1H), 3.56 - 3.38 (m, 6H), 3.34 (s, 3H), 3.28 - 3.16 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 3.00 - 2.94 (m, 1H), 2.88 - 2.80 (m, 1H), 2.78 - 2.67 (m, 1H), 2.17 - 1.96 (m, 6H), 1.95 - 1.79 (m, 7H), 1.76 - 1.64 (m, 2H), 1.32 (s, 6H).

Example 63





Step 1

To a stirred solution of compound **63-1** (2.5 g, 6.95 mmol) in dry THF (30 mL) was added lithium bis(trimethylsilyl)amide (3.49 g, 20.86 mmol, 1 M in THF) at -70 °C under nitrogen atmosphere and the mixture was stirred at -70 °C for 1 hour. Then 1,1-bis-(bromomethyl)-cyclopropane (4.75 g, 20.86 mmol) was added at -70 °C, and the reaction was stirred at 25 °C for 12 hours. The reaction was quenched with saturated NH_4Cl solution (30 mL), extracted wtih EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **63-2A** and compound **63-2B**. compound **63-2A** (PE:EtOAc = 8:1, Rf = 0.0.45). compound **63-2B** (PE:EtOAc = 8:1, Rf = 0.5).

compound **63-2A**: MS m/z = 507.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.46 - 4.38 (m, 1H), 3.71 -3.59 (m, 5H), 3.36 - 3.24 (m, 1H), 3.05 - 2.92 (m, 1H), 2.83 - 2.76 (m, 1H), 2.40 - 2.29 (m, 1H), 2.12 - 2.05 (m, 1H), 1.67 - 1.57 (m, 1H), 1.40 - 1.37 (m, 9H), 0.96 - 0.91 (m, 1H), 0.87 - 0.82 (m, 9H), 0.76 - 0.71 (m, 1H), 0.65 - 0.46 (m, 2H),0.18 - 0.00 (m, 6H).

compound **63-2B**: MS m/z = 507.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.50 - 4.44 (m, 1H), 4.14 -

4.03 (m, 1H), 3.89 - 3.71 (m, 1H), 3.69 (m, 3H), 3.23 - 3.14 (m, 2H), 2.75 - 2.67 (m, 1H), 2.50 - 2.16 (m, 2H), 1.93 - 1.87(m, 1H), 1.45 - 1.42 (m, 9H), 0.87 (s, 9H), 0.85 - 0.51 (m, 4H), 0.05 (s, 6H).

Step 2

To a stirred solution of compound **63-2B** (200 mg, 0.39 mmol) in DCM (2 mL) was added HCl (2 mL, 4 M in dioxane) and the mixture was stirred at 25 °C for 15 hours. The reaction was concentrated under reduced pressure to afford compound **63-3B** as HCl salt. MS m/z = 292.04 $[M+H]^+$.

Step 3

To a stirred solution of compound **63-3B** (193 mg, HCl salt) in acetonitrile (2 mL) was added potassium carbonate (270 mg, 1.95 mmol) and the mixture was stirred at 25 °C for 12 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **63-4B**. MS m/z = 212.17 $[M+H]^+$.

Step 4

To a stirred solution of compound **63-4B** (180 mg, 0.85 mmol) in dry DCM (5 mL) was added diethylaminosulfur trifluoride (412.02 mg, 2.56 mmol) at -78 °C and the mixture was stirred at -78 °C for 4 hours under nitrogen atmosphere. The reaction was quenched with water (10 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **63-5B**. MS m/z = 214.14 $[M+H]^+$.

Step 5

To a stirred solution of compound **63-5B** (30 mg, 0.14 mmol) in dry THF (3 mL) was added lithium aluminum hydride (10.69 mg, 0.28 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 0.5 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **63-6B**. MS m/z = 186.18 $[M+H]^+$.

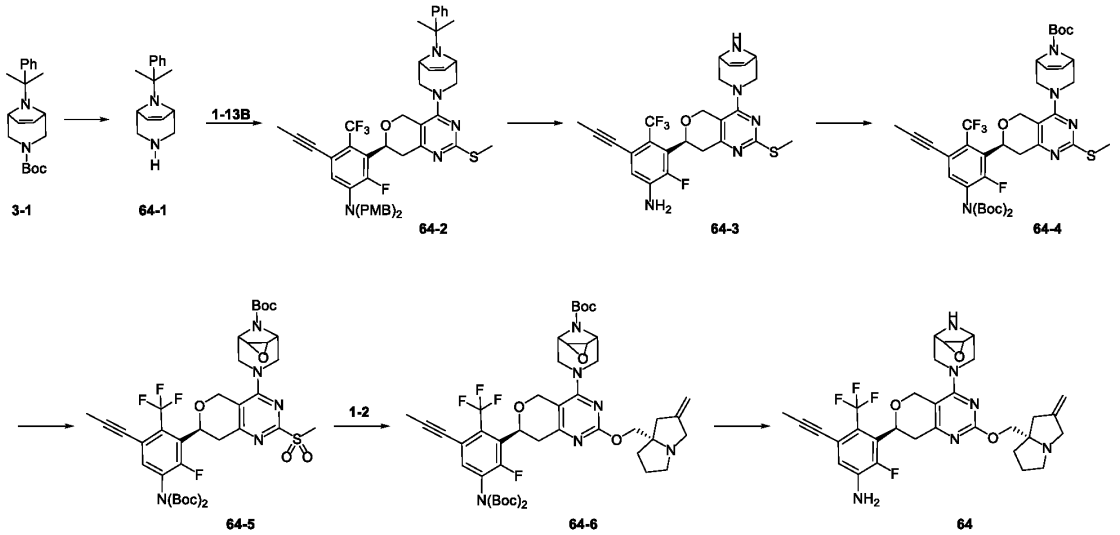
Step 6

To a stirred solution of compound **63-6B** (20 mg, 0.10 mmol) in dry THF (10 mL) was added sodium hydride (5.18 mg, 0.21 mmol, 60% purity) and the mixture was stirred at 25 °C for 0.5 hours under nitrogen atmosphere. Then the solution of compound **4-2** (93 mg, 0.10 mmol) in dry THF (1 mL) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was diluted with EtOAc (20 mL), washed wtih brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **63-7B**. MS m/z = 985.7 $[M+H]^+$.

Step 7

The mixture of compound **63-7B** (15 mg, 0.03 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at 25 °C for 2 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% HCl); Gradient: (ACN): 10%-40%) to afford compound **63** as HCl salt. MS m/z = 645.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 (d, J = 8.0 Hz, 1H), 5.65 (d, J = 52.0 Hz, 1H), 5.27 - 5.16 (m, 1H), 5.00 - 4.87 (m, 5H), 4.27 - 4.20 (m, 2H), 4.05 - 3.87 (m, 4H), 3.68 - 3.65 (m, 1H), 3.59 - 3.53 (m, 2H), 3.47 - 3.37 (m, 1H), 3.07 - 3.03 (m, 1H), 2.81 - 2.64 (m, 3H), 2.23 - 2.09 (m, 4H), 2.02-1.97 (m, 4H), 0.88 (s, 4H).

Example 64



Step 1

A solution of compound **3-1** (2.0 g, 6.09 mmol) in HCl (20 mL, 4 M in dioxane) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure to afford compound **64-1**. MS m/z = 229.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **64-1** (650 mg, 2.85mmol) in N,N-dimethylformamide (20 mL) was added N,N-diisopropylethylamine (1.0 g, 7.76 mmol) and **1-13B** (2.03 g, 2.59 mmol). The resulting mixture was stirred at 100 °C for 2 hours. The reaction was quenched with water (20 mL), extracted wtih EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **64-2**. MS m/z = 864.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **64-2** (1.34 g, 1.55 mmol) in DCM (18 mL) was added TFA (18 mL) and the mixture was stirred at 40 °C for 48 hours. The reaction was concentrated under reduced pressure to afford compound **64-3**. MS m/z = 506.3 $[M+H]^+$.

Step 4

To a stirred solution of compound **64-3** (900 mg, 1.78 mmol) in DCM (10 mL) was added di-tert-butyl dicarbonate (1.36 g, 6.23 mmol), triethyl amine (900.74 mg, 8.90 mmol) and 4-dimethylaminopyridine (43.50 mg, 356.06 μmol). The reaction was stirred at 25 °C for 16 hours. The reaction was diluted with water (10 mL), extracted wtih DCM (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **64-4**. MS m/z = 806.4 $[M+H]^+$.

Step 5

To a stirred solution of compound **64-4** (170 mg, 210.95 μmol) in DCM (3 mL) was added 3-chloroperoxybenzoic acid (214.13 mg, 1.05 mmol, 85% purity) and the mixture was stirred at 35 °C for 20 hours. The reaction was quenched with saturated solution of sodium sulfite (5 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **64-5**. MS m/z = 854.5 $[M+H]^+$.

Step 6

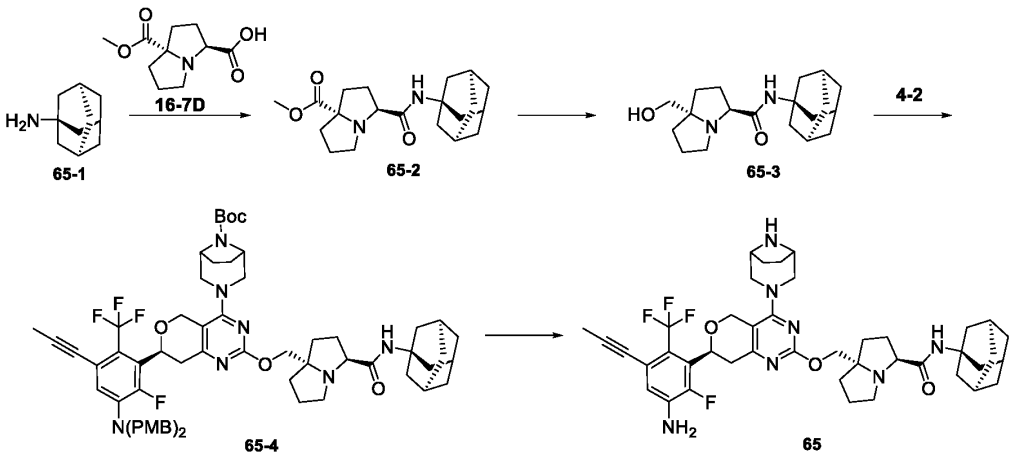
To a stirred solution of compound **1-2** (20 mg, 130.53 μmol) in dry THF (2 mL) was added sodium hydride (7.83 mg, 195.80 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **64-5** (111.46 mg, 130.53 μmol) was added, and the reaction was stirred at 25 °C for 1.5 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **64-6.** MS m/z = 827.6 $[M-100+H]^+$.

Step 7

The mixture of compound **64-6** (45 mg, 48.54 μmol) in TFA (0.4 mL) and DCM (2 mL) was stirred at 25 °C for 1.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: SunFire prep c18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **64**. MS m/z = 627.31 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 5.00 (s, 2H), 4.81 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.17 - 4.11 (m, 2H), 3.75 (d, *J* = 12.0 Hz, 1H), 3.68 (d, *J* = 4.0 Hz, 1H), 3.61 - 3.56 (m, 2H), 3.53 - 3.47 (m, 2H), 3.37 -

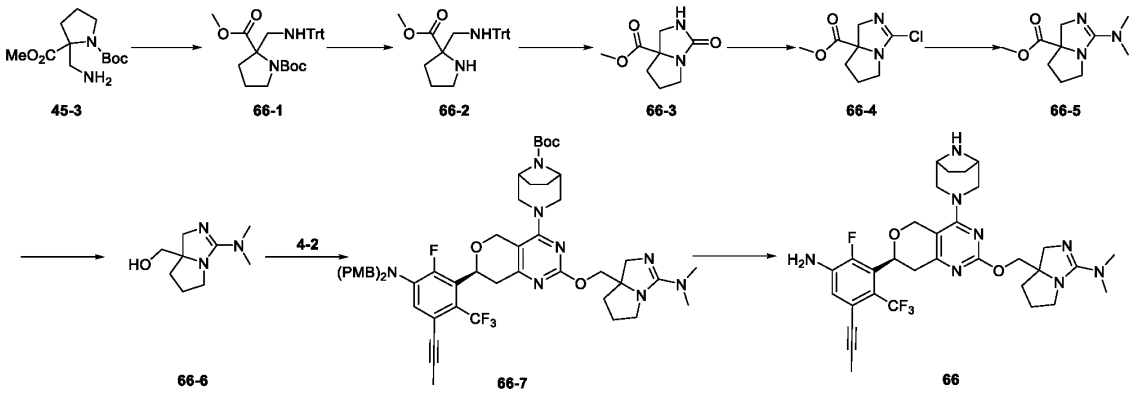
3.36 (m, 1H), 3.24 - 3.13 (m, 4H), 2.84 (d, J = 16.0 Hz, 1H), 2.76 (d, J = 16.0 Hz, 2H), 2.46 (d, J = 16.0 Hz, 1H), 2.14 - 2.09 (m, 1H), 2.02 (s, 3H), 1.99 - 1.89 (m, 2H), 1.86 - 1.81 (m, 1H).

Example 65



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **65-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-72%) to afford compound **65**. MS m/z = 778.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.69 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 3.54 - 3.51 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 20.0 Hz, 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.96 - 2.91 (m, 1H), 2.85 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 2.78 - 2.72 (m, 1H), 2.14 - 2.02 (m, 15H), 1.90 - 1.82 (m, 7H), 1.74 - 1.68 (m, 8H).

Example 66



Step 1

To a stirred solution of compound **45-3** (4.2 g, 16.26 mmol) in dry THF (20 mL) was added triethylamine (1.65 g, 16.26 mmol, 2.27 mL) and trityl chloride (4.53 g, 16.26 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 9:1) to afford compound **66-1**. MS m/z = 501.4 $[M+H]^+$.

Step 2

To a stirred solution of compound **66-1** (6.3 g, 12.58 mmol) in dry DCM (20 mL) was added 2,6-lutidine (2.70 g, 25.17 mmol, 2.92 mL) and trimethylsilyl trifluoromethanesulfonate (4.20 g, 18.88 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. The reaction was quenched with water (50 mL), extracted wtih DCM (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **66-2**. MS m/z = 401.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **66-2** (3 g, 7.49 mmol) in dry THF (15 mL) was added triphosgene (2.22 g, 7.49 mmol) and the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (Flash Spherical C18 column; [ACN-H_2O (0.1%FA)]; Gradient: (ACN): 0%-20%) to afford compound **66-3**. MS m/z = 185.1 $[M+H]^+$.

Step 4

A solution of compound **66-3** (480 mg, 2.61 mmol) in phosphorus oxychloride (5 mL) was stirred at 80 °C for 2 hours. The reaction was concentrated under reduced pressure to afford crude compound **66-4**. MS m/z = 203.1 $[M+H]^+$.

Step 5

To a stirred solution of compound **66-4** (194 mg, crude) in ACN (5 mL) was added potassium carbonate (395.65 mg, 2.88 mmol) and dimethyl amine (129.48 mg, 2.88 mmol, 2 M in THF). The mixture was stirred at 80 °C for 12 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 5:1) to afford compound **66-5**. MS m/z = 212.1 $[M+H]^+$.

Step 6

To a stirred solution of compound **66-5** (70 mg, 331.34 μmol) in MeOH (2 mL) was added lithium chloride (28.09 mg, 662.69 μmol) and sodium borohydride (25.07 mg, 662.69 μmol). The mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The

residue was purified by flash chromatography (Flash Spherical C18 column; [ACN-H_2O (0.1%FA)]; Gradient: (ACN): 0%-20%) to afford compound **66-6**. MS m/z = 184.3 $[M+H]^+$.

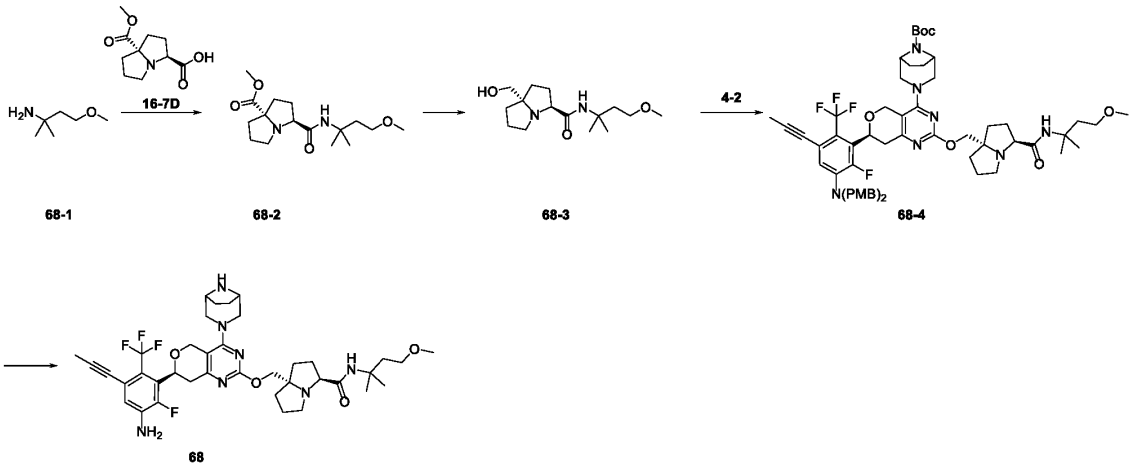
Step 7

To a stirred solution of compound **66-6** (65 mg, 354.71 μmol) in dry THF (1 mL) was added sodium hydride (17.02 mg, 709.41 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 30 minutes. Then compound **4-2** (312.13 mg, 354.71 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **66-7**. MS m/z = 983.7 $[M+H]^+$.

Step 8

The mixture of compound **66-7** (45 mg, 45.77 μmol) in TFA (1 mL) and DCM (1 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: SunFire prep C18, 250*19mm, 5μm; ACN-H_2O (0.1%FA); Gradient: (ACN): 20%-70%) to afford compound **66** as FA salt. MS m/z = 643.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 1.28H), 6.93 (d, J = 8.0 Hz, 1H), 5.19 (dd, J = 12.0, 4.0 Hz, 1H), 4.86 - 4.82 (m, 1H), 4.72 (d, J = 12.0 Hz, 1H), 4.47 - 4.34 (m, 2H), 4.25 (t, J = 12.0 Hz, 1H), 4.11 - 4.01 (m, 2H), 3.89 (dd, J = 12.0, 4.0 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.70 - 3.59 (m, 2H), 3.58 - 3.50 (m, 2H), 3.30 - 3.23 (m, 2H), 3.15 - 3.06 (m, 6H), 2.91 (dd, J = 20.0, 4.0 Hz, 1H), 2.29 - 2.13 (m, 4H), 2.11 - 2.01 (m, 6H), 1.99 - 1.90 (m, 1H).

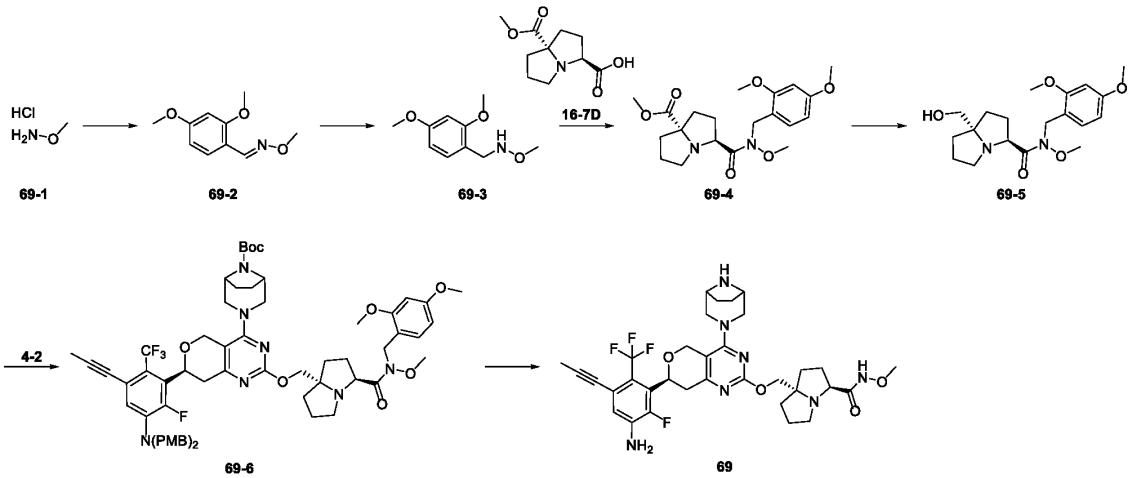
Example 68



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **68-1** as the raw material to obtain crude product. The crude product was purified by Prep-

HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **68**. MS m/z = 744.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 - 5.12 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.11 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.72 - 3.67 (m, 1H), 3.55 - 3.46 (m, 5H), 3.44 - 3.39 (m, 1H), 3.31 (s, 3H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.90 (m, 1H), 2.88 - 2.80 (m, 1H), 2.78 - 2.70 (m, 1H), 2.15 - 1.98 (m, 7H), 1.96 - 1.77 (m, 8H), 1.75 - 1.65 (m, 2H), 1.36 (d, *J* = 8.0 Hz, 6H).

Example 69



Step 1

To a stirred solution of compound **69-1** (1.7 g, 20.46 mmol) in THF (4 mL) and water (12 mL) was added 2,4-dimethoxybenzaldehyde (2 g, 12.04 mmol) and sodium acetate (1.48 g, 18.05 mmol). The resulting mixture was stirred at 25 °C for 3 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were concentrated under reduced pressure to afford compound **69-2**. MS m/z = 196.1 $[M+H]^+$.

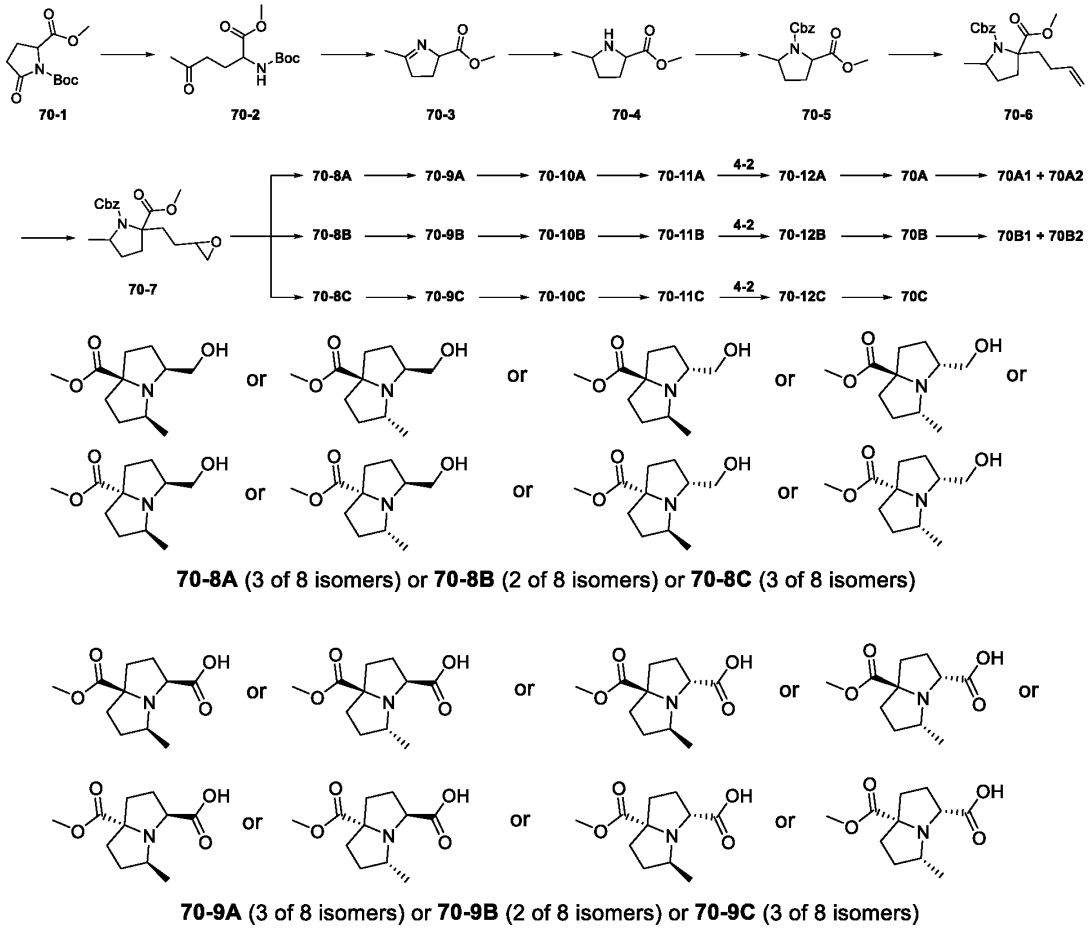
Step 2

To a stirred solution of compound **69-2** (1.00 g, crude) in acetic acid (8 mL) was added sodium cyanoborohydride (644 mg, 10.25 mmol) and the mixture was stirred at 25 °C for 4 hours. Then 2 N sodium hydroxide was added to adjust pH = 9, extracted wtih EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:2) to afford compound **69-3**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm δ 7.17 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 4.0 Hz, 1H), 6.50 - 6.43 (m, 2H), 3.84 (d, *J* = 4.0 Hz, 2H), 3.75 (d, *J* = 8.0 Hz, 6H), 3.37 (s, 3H).

Step 3

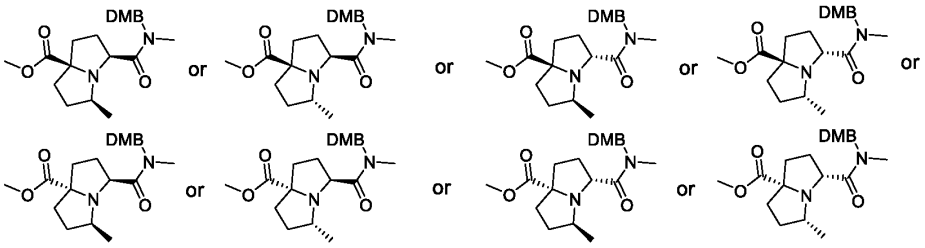
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **69-3** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-75%) to afford compound **69**. MS m/z = 674.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.71 (s, 3H), 3.60 (t, *J* = 8.0 Hz, 1H), 3.57 - 3.49 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.88 - 2.78 (m, 2H), 2.22 - 1.93 (m, 11H), 1.85 - 1.65 (m, 4H).

Example 70

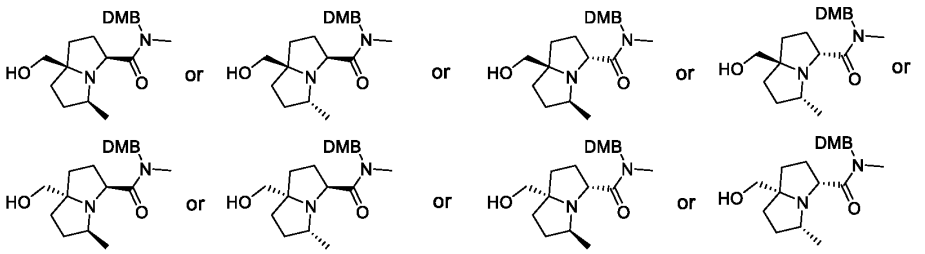


70-8A (3 of 8 isomers) or **70-8B** (2 of 8 isomers) or **70-8C** (3 of 8 isomers)

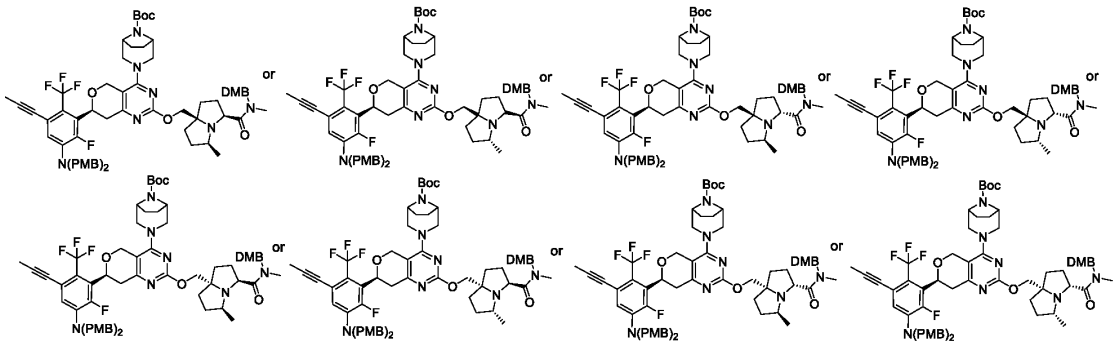
70-9A (3 of 8 isomers) or **70-9B** (2 of 8 isomers) or **70-9C** (3 of 8 isomers)



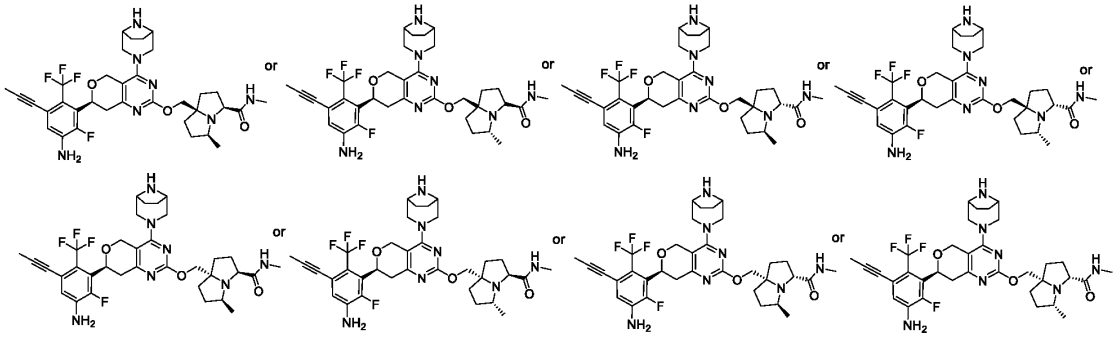
70-10A (3 of 8 isomers) or **70-10B** (2 of 8 isomers) or **70-10C** (3 of 8 isomers)



70-11A (3 of 8 isomers) or **70-11B** (2 of 8 isomers) or **70-11C** (3 of 8 isomers)



70-12A (3 of 8 isomers) or **70-12B** (2 of 8 isomers) or **70-12C** (3 of 8 isomers)



70A1 (single isomer) or **70A2** (mixture of 3 isomers) or **70B1** (single isomer) or **70B2** (mixture of 2 isomers) or **70C** (mixture of 3 isomers)

Step 1

To a stirred solution of compound **70-1** (2.00 g, 8.22 mmol) in THF (15 mL) was added methylmagnesium bromide (3.56 mL, 12.69 mmol, 3 M in THF) at 0 °C and the mixture was stirred at 25 °C for 12 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL) at 0 °C, extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (3 × 10

mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 8:1) to afford compound **70-2**. MS m/z = 160.3 $[M\text{-Boc}+H]^+$.

Step 2

To a stirred solution of compound **70-2** (4.00 g, 15.43 mmol) in DCM (5 mL) was added TFA (5 mL) and the mixture was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure to afford crude compound **70-3**. MS m/z = 142.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **70-3** (120 mg, crude) in dry ethanol (5 mL) was added Pd/C (12 mg, 10% purity) and the mixture was stirred at 25 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was concentrated under reduced pressure to afford crude compound **70-4**.MS m/z = 144.1 $[M+H]^+$.

Step 4

To a stirred solution of compound **70-4** (120 mg, 0.84 mmol) and potassium carbonate (173 mg, 1.26 mmol) in acetonitrile (15 mL) was added benzyl chloroformate (172 mg, 1.01 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 2 hours. The reaction was quenched with ice water (1 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **70-5**. MS m/z = 278.3 $[M+H]^+$.

Step 5

To a stirred solution of compound **70-5** (150 mg, 0.54 mmol) in dry THF (10 mL) was added lithium bis(trimethylsilyl)amide (0.65 mL, 0.65 mmol, 1 M in THF) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then 4-bromo-1-butene (88 mg, 0.65 mmol) was added at 0 °C, and the reaction was stirred at 25 °C for 6 hours. The reaction was quenched with saturated NH_4Cl solution (2 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 30:1) to afford compound **70-6**. MS m/z = 332.2 $[M+H]^+$.

Step 6

To a stirred solution of compound **70-6** (500 mg, 1.51 mmol) in DCM (10 mL) was added 3-chloroperoxybenzoic acid (781 mg, 4.53 mmol) at 0 °C and the mixture was stirred at 25 °C for 6 hours. The reaction was quenched with saturated solution of sodium sulfite (10 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over

anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **70-7**. MS m/z = 348.2 $[M+H]^+$.

Step 7

To a stirred solution of compound **70-7** (1.60 g, 4.61 mmol) in dry MeOH (10 mL) was added Pd/C (100 mg, 10% purity) and the mixture was stirred at 25 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **70-8A** (3 of 8 isomers) (DCM:MeOH = 15:1, Rf = 0.6) and compound **70-8B** (2 of 8 isomers) (DCM:MeOH = 15:1, Rf = 0.5) and compound **70-8C** (3 of 8 isomers) (DCM:MeOH = 15:1, Rf = 0.2). MS m/z = 214.2 $[M+H]^+$.

Step 8

To a stirred solution of compound **70-8A** (180 mg, 843.99 μmol) in a 4 mL mixted solvents (ACN:H_2O = 100:0.75) was added chromium trioxide (28.13 mg, 281.33 μmol) and periodic acid (534.39 mg, 2.34 mmol) at 0 °C and the mixture was stirred at 25 °C for 16 hours. The reaction was filtered, the filter was concentrated under reduced pressure to afford compound **70-9A**. MS m/z = 228.1 $[M+H]^+$.

With reference to step 8, compound **70-8A** was replaced with compound **70-8B** or **70-8C** as the raw material to obtain compound **70-9B**, MS m/z = 228.1 $[M+H]^+$ or compound **70-9C**, MS m/z = 228.1 $[M+H]^+$ respectively.

Step 9

To a stirred solution of compound **70-9A** (200 mg, 0.80 mmol) in N,N-dimethylformamide (4 mL) was added N,N-diisopropylethylamine (227 mg, 1.76 mmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (435 mg, 1.14 mmol) and 1-(3,4-dimethoxyphenyl)-N-methylmethanamine (160 mg, 0.80 mmol). The mixture was stirred at 25 °C for 6 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **70-10A**. MS m/z = 391.3 $[M+H]^+$.

With reference to step 9, compound **70-9A** was replaced with compound **70-9B** or **70-9C** as the raw material to obtain compound **70-10B**, MS m/z = 391.3 $[M+H]^+$ or compound **70-10C**, MS m/z = 391.3 $[M+H]^+$ respectively.

Step 10

To a stirred solution of compound **70-10A** (200.00 mg, 0.51 mmol) in MeOH (4 mL) was added sodium methoxide (55 mg, 1.02 mmol) and sodium borohydride (194 mg, 5.12 mmol) at 0 °C. The mixture was stirred at 60 °C for 16 hours. The reaction was quenched with sodium sulfate decahydrate

(1.0 g), filered, the filtrate was concentrated under reduced pressure to afford compound **70-11A**. MS m/z = 363.3 $[M+H]^+$.

With reference to step 10, compound **70-10A** was replaced with compound **70-10B** or **70-10C** as the raw material to obtain compound **70-11B**, MS m/z = 363.3 $[M+H]^+$ or compound **70-11C**, MS m/z = 363.3 $[M+H]^+$ respectively.

Step 11

To a stirred solution of compound **70-11A** (40.28 mg, 111.12 μmol) in dry THF (4 mL) was added sodium hydride (4.44 mg, 185.19 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 1 hour. Then compound **4-2** (80 mg, 92.60 μmol) was added, and the reaction was stirred at 25 °C for 4 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **70-12A**. MS m/z = 1162.8 $[M+H]^+$.

With reference to step 11, compound **70-11A** was replaced with compound **70-11B** or **70-11C** as the raw material to obtain compound **70-12B**, MS m/z = 1162.8 $[M+H]^+$ or compound **70-12C**, MS m/z = 1162.8 $[M+H]^+$ respectively.

Step 12

To a solution of compound **70-12A** (30 mg, 25.81 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 10%-35%) to afford compound **70A1** (single isomer) as FA salt and compound **70A2** (mixture of 3 isomers) as FA salt. HPLC Analysis methods (chromatographic column: Agilent InfinityLab Poroshell 120 EC-C18 4.6*100mm 2.7um); Mobile phase: A: 90% (5 mM potassium phosphate monobasic)-10%ACN; B: 90%ACN-10%H_2O; Gradient: B%: 0 - 85%, 9 min). Compound **70A1**, Rt = 5.792 mins; compound **70A2**, Rt = 6.000 mins (peak 1) + 6.089 mins (peak 2)+ 11.8 mins (peak 3).

Compound **70A1** (single isomer)**:** MS m/z = 672.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.49 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (s, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.24 - 4.16 (m, 2H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.98 (s, 2H), 3.69 (d, *J* = 12.0 Hz, 1H), 3.55 (d, *J* = 16.0 Hz, 1H), 3.39 - 3.34 (m, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 2H), 2.96 - 2.84 (m, 2H), 2.74 (s, 3H), 2.38 - 2.30 (m, 1H), 2.22 (t, *J* = 12.0 Hz, 1H), 2.11 - 1.91 (m, 10H), 1.78 - 1.64 (m, 3H), 1.11 (d, *J* = 8.0 Hz, 3H). Compound **70A2** (mixture of 3 isomers): MS m/z = 672.5 $[M+H]^+$.^1H NMR (400 MHz, CD_3OD) δ ppm 8.46 (s, 2.98H), 7.01 - 6.84 (m, 1H), 5.18 - 5.06 (m, 2H), 4.80 - 4.68 (m, 1H), 4.63 - 4.51 (m, 1H), 4.23 - 3.99 (m, 6H), 3.87 - 3.71 (m, 1H), 3.64 - 3.50 (m, 1H), 3.38 - 3.35 (m,

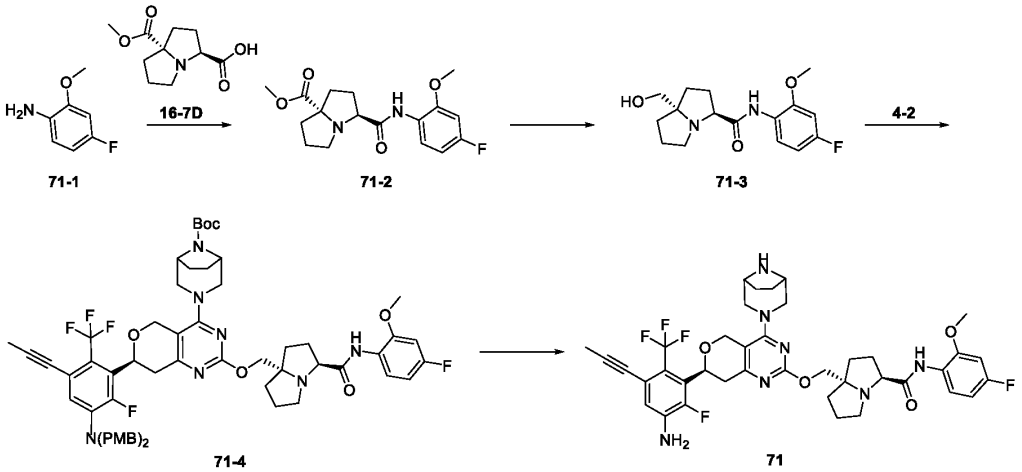
1H), 3.15 - 3.09 (m, 1H), 2.95 - 2.90 (m, 1H), 2.76 - 2.75 (m, 3H), 2.37 - 2.28 (m, 1H), 2.12 - 1.93 (m, 11H), 1.77 - 1.66 (m, 3H), 1.13 - 1.10 (m, 3H).

To a solution of compound **70-12B** (40 mg, 34.41 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters SunFire, 250*19mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 12%-28%) to afford compound **70B1** (single isomer) as FA salt and compound **70B2** (mixture of 2 isomers) as FA salt. HPLC Analysis methods (chromatographic column: Agilent InfinityLab Poroshell 120 EC-C18 4.6*100mm 2.7um); Mobile phase: A: 90% (5 mM potassium phosphate monobasic)-10%ACN; B: 90%ACN-10%H_2O; Gradient: B%: 0 - 85%, 9 min). Compound **70B1**, Rt = 3.517 mins; compound **70B2**, Rt = 3.524 mins (peak 1) + 3.550 mins (peak 2).

Compound **70B1** (单一异构体) **:** MS m/z= 672.5 $[M+H]^+$.^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.48 (s, 1.21H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.82 (s, 1H), 4.71 (d, *J* = 16.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.19 (dd, *J* = 20.0, 12.0 Hz, 2H), 4.03 (s, 2H), 3.78 - 3.63 (m, 2H), 3.58 (d, *J* = 13.5 Hz, 1H), 3.37 (s, 1H), 3.24 (dd, *J* = 20.0, 12.0 Hz, 2H), 2.90 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.73 (s, 3H), 2.29 - 2.14 (m, 3H), 2.02 (s, 5H), 1.97 - 1.90 (m, 1H), 1.85 (d, *J* = 12.0 Hz, 2H), 1.80 - 1.74 (m, 2H), 1.70 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.54 (q, *J* = 12.0, 8.0 Hz, 1H), 1.14 (d, *J* = 8.0 Hz, 3H). Compound **70B2** (mixture of 2 isomers) **:** MS m/z = 672.5 $[M+H]^+$.^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.47 (s, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.16 (m, 1H), 4.82 (s, 1H), 4.73 - 4.68 (m, 1H), 4.38 - 4.13 (m, 3H), 4.05 (s, 2H), 3.76 - 3.57 (m, 3H), 3.39 - 3.34 (m, 1H), 3.26 - 3.20 (m, 2H), 2.93 - 2.86 (m, 1H), 2.74 - 2.73 (m, 3H), 2.28 - 2.18 (m, 2H), 2.10 - 1.95 (m, 7H), 1.89 - 1.66 (m, 5H), 1.59 - 1.49 (m, 1H), 1.15 - 1.10 (m, 3H).

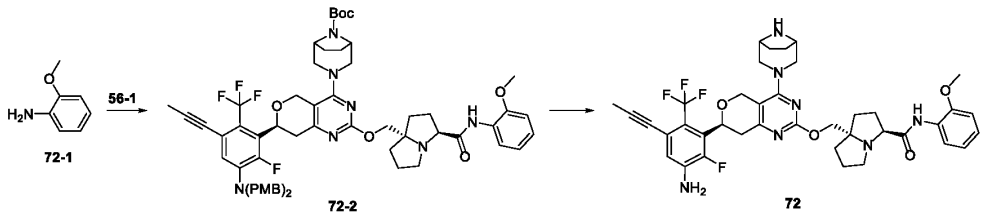
To a solution of compound **70-12C** (28 mg, 24.09 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 35%-80%) to afford compound **70C** (mixture of 3 isomers). MS m/z = 672.5 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 4.07 - 4.00 (m, 2H), 3.66 - 3.64 (m, 1H), 3.55 - 3.48 (m, 3H), 3.43 - 3.40 (m, 1H), 3.24 - 3.14 (m, 2H), 3.05 - 3.02 (m, 1H), 2.87 - 2.81 (m, 1H), 2.73 (s, 3H), 2.13 - 1.98 (m, 9H), 1.92 - 1.89 (m, 1H), 1.85 - 1.80 (m, 2H), 1.74 - 1.63 (m, 3H), 1.03 (d, *J* = 4.0 Hz, 3H).

Example 71



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **71-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-80%) to afford compound **71**. MS m/z = 768.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.17 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.90 (d, *J* = 12.0 Hz, 1H), 6.80 (dd, *J* = 12.0, 4.0 Hz, 1H), 6.65 (td, *J* = 8.0, 4.0 Hz, 1H), 5.10 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 8.0 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.69 (s, 3H), 3.49 - 3.40 (m, 4H), 3.23 - 3.16 (m, 1H), 3.13 - 3.06 (m, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.81 - 2.74 (m, 2H), 2.40 - 2.31 (m, 1H), 2.19 - 2.09 (m, 2H), 2.04 - 1.69 (m, 12H), 1.61 - 1.52 (m, 1H).

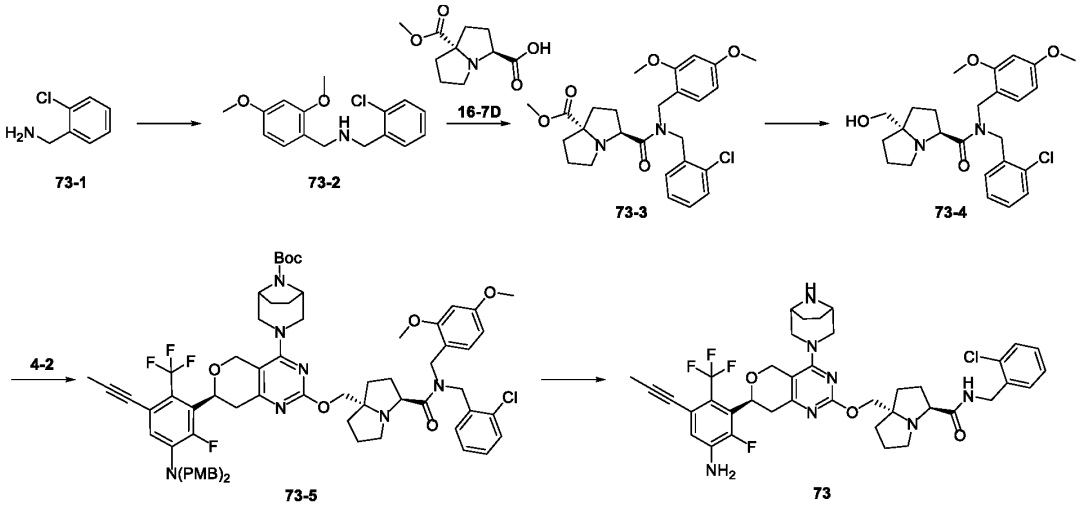
Example 72



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **72-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 55%-80%) to afford compound **72**. MS m/z = 750.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 (d, *J* = 8.0 Hz, 1H), 7.09 - 7.04 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.94 - 6.89 (m, 2H), 5.11 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.72 (s, 3H), 3.49 - 3.40 (m, 4H), 3.25 - 3.19 (m, 1H), 3.13 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.89 (d, *J* = 12.0 Hz, 1H), 2.82 - 2.74 (m,

2H), 2.41 - 2.34 (m, 1H), 2.16 - 1.94 (m, 9H), 1.87 (t, *J* = 8.0 Hz, 1H), 1.82 - 1.77 (m, 2H), 1.75 - 1.69 (m, 2H), 1.58 - 1.53 (m, 1H).

Example 73



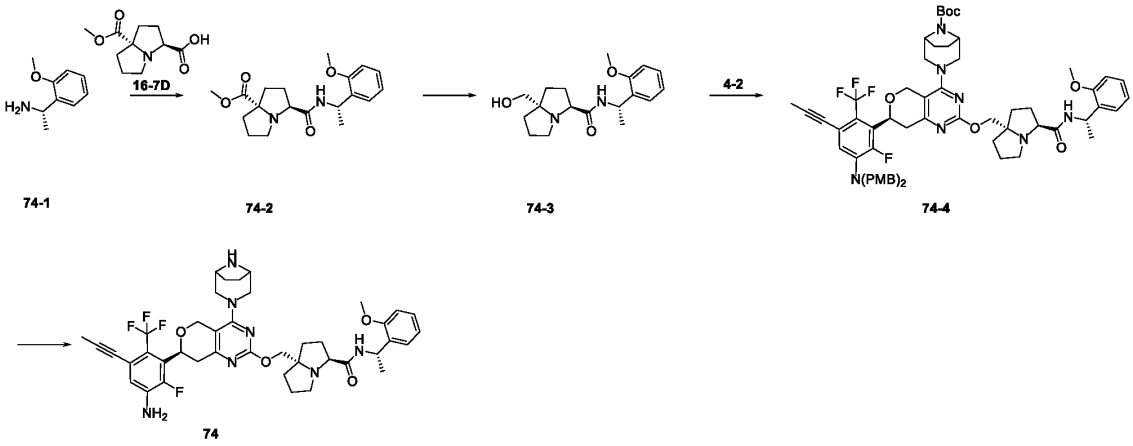
Step 1

To a stirred solution of compound **73-1** (1 g, 7.06 mmol) in dry MeOH (10 mL) was added 2,4-dimethoxybenzaldehyde (1.41 g, 8.47 mmol), sodium cyanoborohydride (1.33 g, 21.19 mmol) and acetic acid (42.41 mg, 706.23 μmol). The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **73-2**. MS m/z = 292.1 $[M+H]^+$.

Step 2

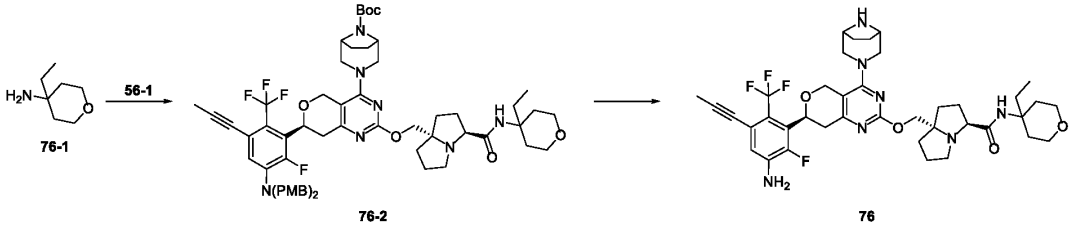
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **73-2** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18, 150*40mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 35%-70%) to afford compound **73**. MS m/z = 768.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.41 (td, *J* = 8.0, 4.0 Hz, 2H), 7.31 - 7.24 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.83 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.53 - 3.50 (m, 3H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.03 (d, *J* = 16.0 Hz, 1H), 2.93 - 2.87 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.78 - 2.72 (m, 1H), 2.15 - 2.06 (m, 2H), 2.06 - 1.98 (m, 5H), 1.97 - 1.86 (m, 4H), 1.85 - 1.79 (m, 2H), 1.76 - 1.65 (m, 2H).

Example 74



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **74-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **74**. MS m/z = 778.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.27 - 7.20 (m, 2H), 6.98 - 6.87 (m, 3H), 5.34 - 5.29 (m, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.24 - 4.03 (m, 3H), 3.85 (s, 3H), 3.83 - 3.77 (m, 1H), 3.61 - 3.39 (m, 4H), 3.27 - 3.10 (m, 2H), 3.08 - 2.95 (m, 2H), 2.90 - 2.74 (m, 2H), 2.16 - 2.05 (m, 2H), 2.02 (s, 3H), 1.98 - 1.80 (m, 7H), 1.78 - 1.66 (m, 2H), 1.42 (d, *J* = 4.0 Hz, 3H).

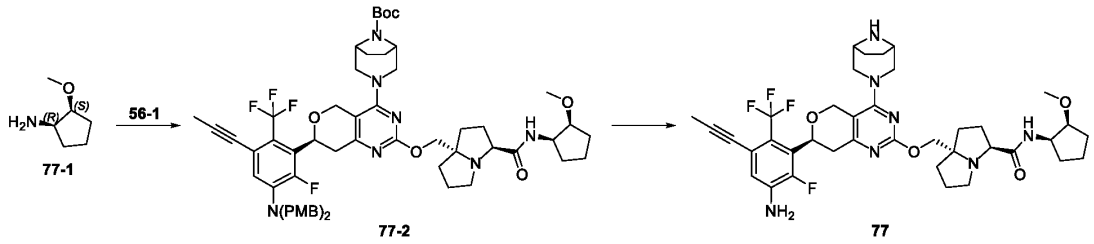
Example 76



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **76-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **76**. MS m/z = 756.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.17 (t, *J* = 12.0 Hz, 2H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.83 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.78 - 3.71 (m, 2H), 3.68 - 3.63 (m, 2H), 3.54 (d, *J* = 12.0 Hz, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 3.02 - 2.95 (m, 1H), 2.88 - 2.79 (m,

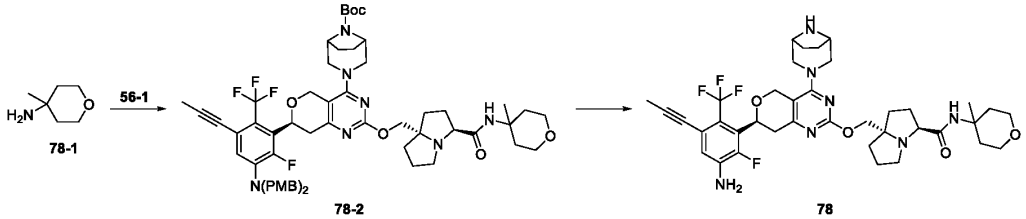
2H), 2.20 - 2.06 (m, 4H), 2.05 - 1.83 (m, 12H), 1.77 - 1.68 (m, 3H), 1.63 - 1.53 (m, 2H), 0.86 (t, *J* = 8.0 Hz, 3H).

Example 77



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **77-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **77**. MS m/z = 742.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.06 (m, 4H), 3.84 - 3.80 (m, 1H), 3.72 - 3.69 (m, 1H), 3.58 - 3.53 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.30 (s, 3H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.07 - 3.00 (m, 2H), 2.85 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.17 - 2.10 (m, 2H), 2.07 - 1.88 (m, 10H), 1.88 - 1.80 (m, 3H), 1.79 - 1.70 (m, 4H), 1.65 - 1.56 (m, 2H).

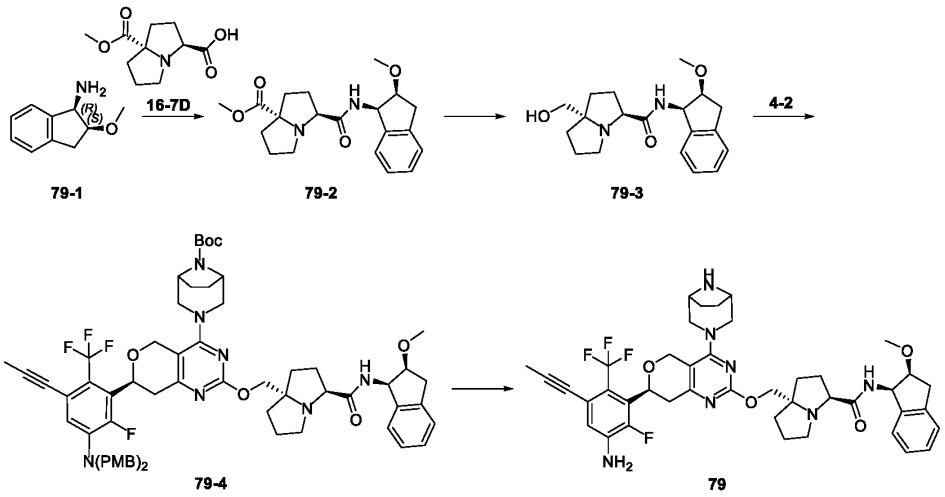
Example 78



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **78-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 28%-36%) to afford compound **78**. MS m/z = 742.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.79 - 3.76 (m, 1H), 3.74 - 3.64 (m, 4H), 3.54 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.98 - 2.94 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.79 - 2.73 (m, 1H), 2.16 - 2.06 (m, 4H), 2.03 - 1.99 (m, 4H), 1.94 - 1.87 (m, 5H), 1.83 (s, 2H), 1.77 - 1.67 (m, 2H), 1.66 - 1.59 (m, 2H),

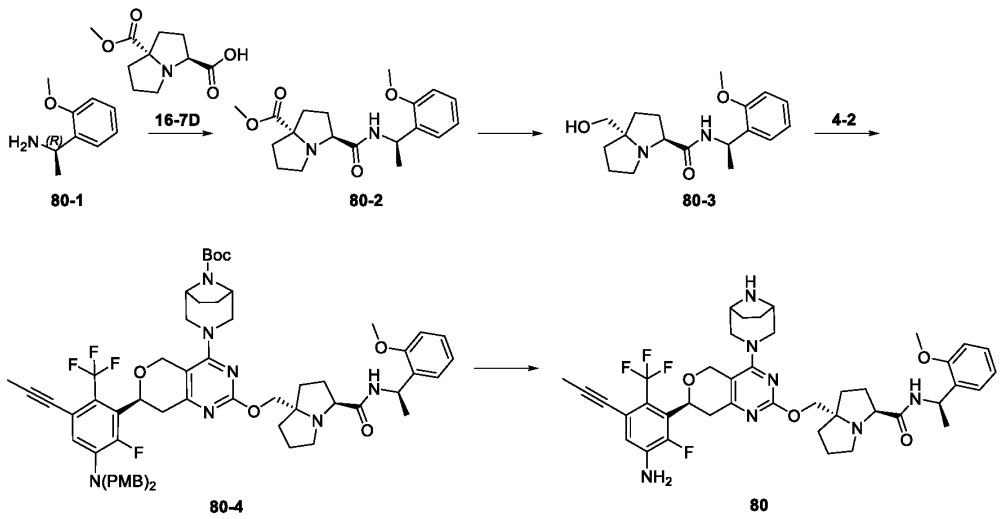
1.40 (s, 3H).

Example 79



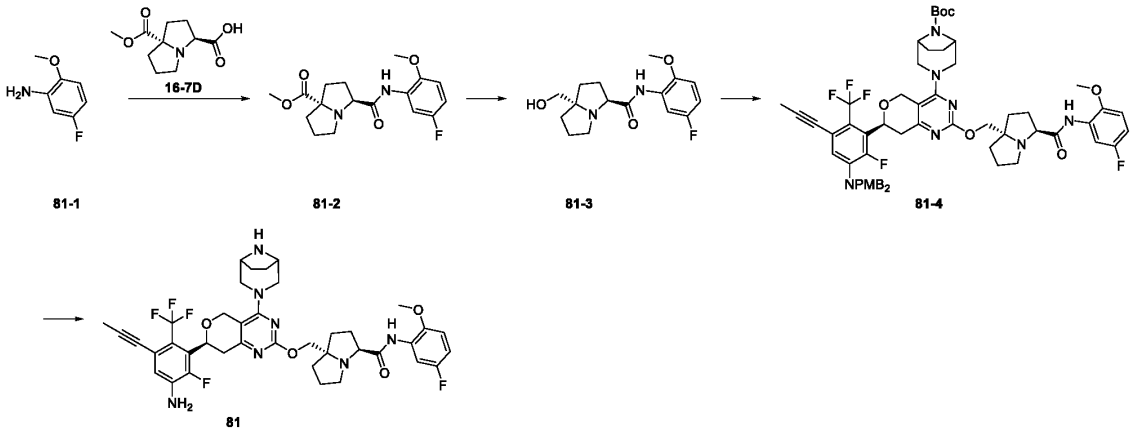
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **79-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-90%) to afford compound **79**. MS m/z = 790.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.23 - 7.08 (m, 4H), 6.90 (d, *J* = 12.0 Hz, 1H), 5.45 - 5.32 (m, 1H), 5.14 - 5.07 (m, 1H), 4.80 - 4.74 (m, 1H), 4.61 (t, *J* = 16.0 Hz, 1H), 4.19 - 3.83 (m, 5H), 3.51 - 3.40 (m, 3H), 3.38 (s, 3H), 3.24 - 2.99 (m, 5H), 2.85 - 2.43 (m, 3H), 2.20 - 2.12 (m, 2H), 2.07 - 1.85 (m, 9H), 1.80 - 1.54 (m, 4H).

Example 80



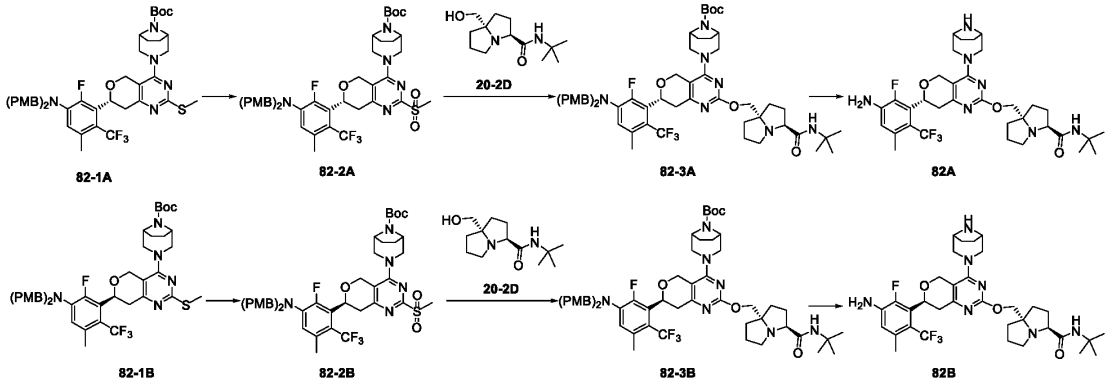
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **80-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-70%) to afford compound **80**. MS m/z = 778.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.32 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.25 - 7.20 (m, 1H), 6.96 - 6.89 (m, 3H), 5.34 (q, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.80 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.55 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.81 - 2.75 (m, 1H), 2.67 - 2.59 (m, 1H), 2.14 - 2.05 (m, 2H), 2.04 - 1.95 (m, 5H), 1.94 - 1.89 (m, 2H), 1.87 - 1.77 (m, 4H), 1.73 - 1.64 (m, 2H), 1.41 (d, *J* = 8.0 Hz, 3H).

Example 81



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **81-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **81**. MS m/z = 768.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.98 (dd, *J* = 12.0, 4.0 Hz, 1H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.83 - 6.78 (m, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.79 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.10 (m, 2H), 4.03 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.88 (s, 3H), 3.58 - 3.54 (m, 3H), 3.49 - 3.43 (m, 1H), 3.27 - 3.20 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 3.01 - 2.98 (m, 1H), 2.86 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.80 - 2.73 (m, 1H), 2.22 - 2.14 (m, 2H), 2.06 - 2.02 (m, 5H), 1.97 - 1.90 (m, 4H), 1.88 - 1.81 (s, 2H), 1.80 - 1.72 (m, 2H).

Example 82



Step 1

To a stirred solution of compound **82-1A** (700 mg, 0.85 mmol) in THF (10 mL) was added 3-chloroperoxybenzoic acid (344.96 mg, 1.70 mmol, 85% purity) at 0 °C and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with 5% sodium thiosulfate (4 mL), extracted wtih DCM (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **82-2A**. MS m/z = 856.5 $[M+H]^+$.

With reference to step 1, compound **82-1A** was replaced with compound **82-1B** as the raw material to obtain compound **82-2B**. MS m/z = 856.5 $[M+H]^+$.

Step 2

To a stirred solution of **20-2D** (30.89 mg, 0.13 mmol) in dry THF (5 mL) was added sodium hydride (25.72 mg, 0.64 mmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours. Then the solution of compound **82-2A** (110 mg, 0.13 mmol) in dry THF (5 mL) was added and the resulting mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (5 mL), extracted wtih EtOAc (2 × 6 mL). The combined organic layers were washed with brine (8 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **82-3A**. MS m/z = 1016.7 $[M+H]^+$.

With reference to step 6, compound **82-2A** was replaced with compound **82-2B** as the raw material to obtain compound **82-3B**. MS m/z = 1016.7 $[M+H]^+$.

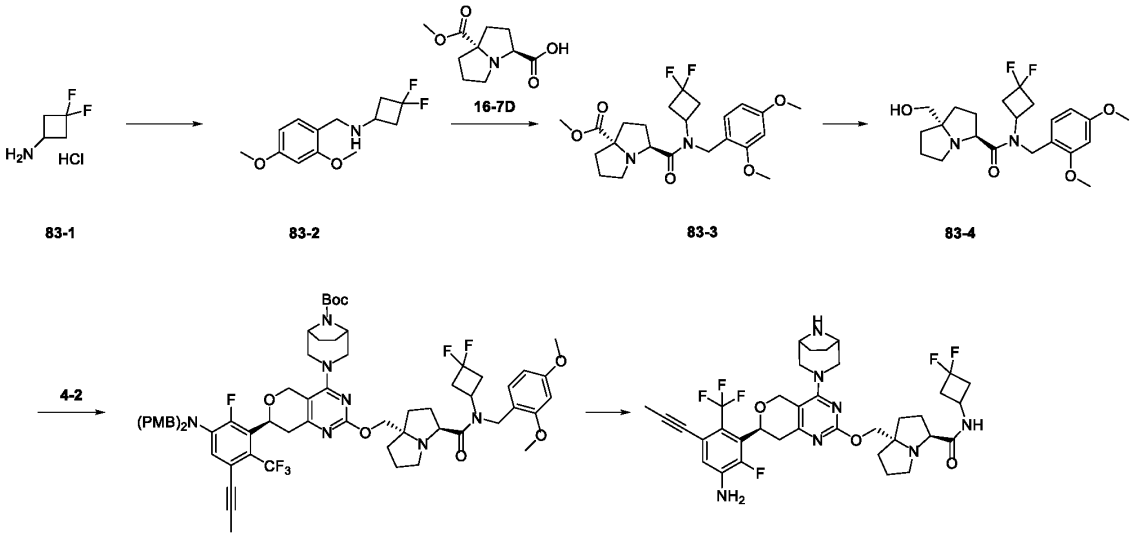
Step 3

A solution of compound **82-3A** (105 mg, 0.11 mmol) in TFA (5 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **82A**. MS m/z = 676.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.68 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.13 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* =

12.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.56 - 3.47 (m, 3H), 3.45 - 3.39 (m, 1H), 3.29 - 3.20 (m, 1H), 3.04 (d, J = 16.0 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.89 - 2.80 (m, 1H), 2.79 - 2.70 (m, 1H), 2.39 - 2.32 (m, 3H), 2.15 - 2.04 (m, 2H), 2.04 - 1.97 (m, 1H), 1.95 - 1.80 (m, 7H), 1.76 - 1.65 (m, 2H), 1.36 (s, 9H).

A solution of compound **82-3B** (120 mg, 0.11 mmol) in TFA (5 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **82B**. MS m/z = 676.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.68 (d, J = 8.0 Hz, 1H), 5.21 - 5.13 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.07 (d, J = 8.0 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.57 - 3.47 (m, 3H), 3.45 - 3.38 (m, 1H), 3.28 - 3.18 (m, 1H), 3.07 - 2.99 (m, 1H), 2.95 - 2.82 (m, 2H), 2.78 - 2.69 (m, 1H), 2.39 - 2.32 (m, 3H), 2.16 - 1.97 (m, 3H), 1.96 - 1.79 (m, 7H), 1.75 - 1.64 (m, 2H), 1.35 (s, 9H).

Example 83



Step 1

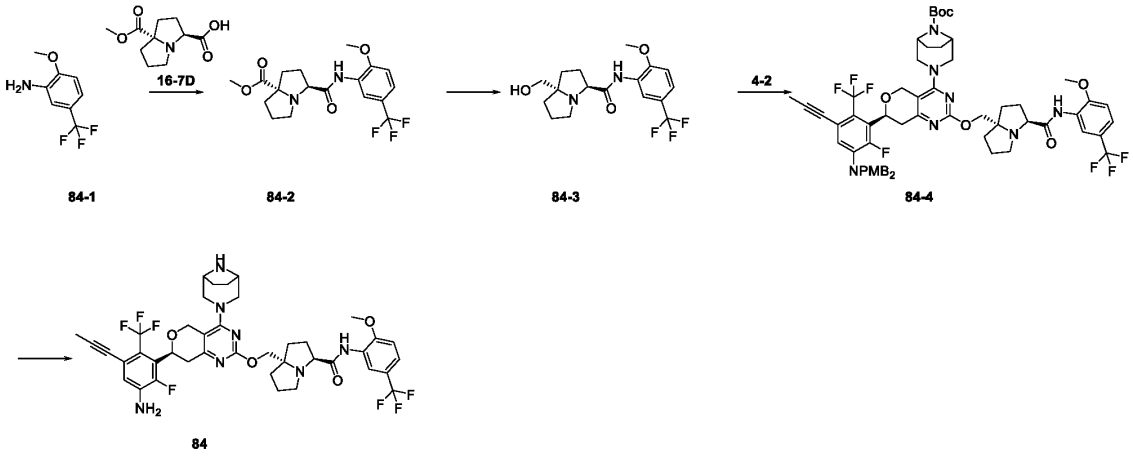
To a stirred solution of compound **83-1** (100 mg, 696,56μmol) in MeOH (1 mL) was added 2,4-dimethoxybenzaldehyde (104.17 mg, 626.90 μmol) and the mixture was stirred at 25 °C for 0.5 hours. Then sodium cyanoborohydride (87.55 mg, 1.39 mmol) was added and the resulting mixture was stirred at 25 °C for 15 hours. The reaction was quenched with water (3 mL), extracted wtih EtOAc (3 × 2 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was

purified by flash chromatography (DCM: MeOH = 15:1) to afford compound **83-2**. MS m/z = 258.1 $[M+H]^+$.

Step 2

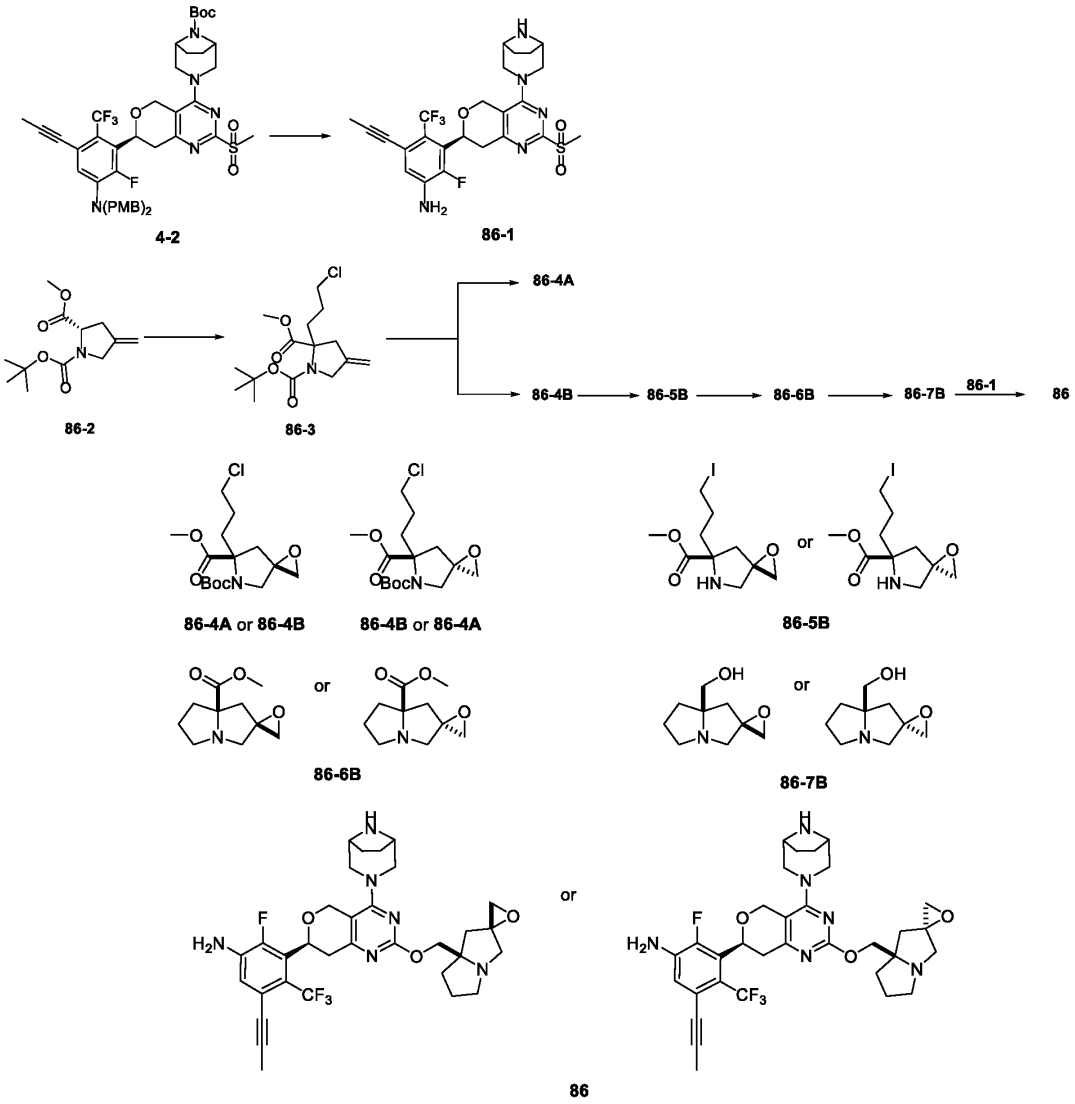
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **83-2** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **83**. MS m/z = 734.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.82 - 4.78 (m, 1H), 4.67 - 6.64 (m, 1H), 4.18 - 4.14 (m, 3H), 4.07 - 4.04 (m, 1H), 3.78 - 3.75 (m, 1H), 3.62 (s, 2H), 3.57 - 3.54 (m, 1H), 3.47 - 3.44 (m, 1H), 3.26 - 3.19 (m, 1H), 3.09 - 3.06 (m, 1H), 2.98 - 2.82 (m, 4H), 2.77 - 2.71 (m, 1H), 2.62 - 2.49 (m, 2H), 2.13 - 2.04 (m, 3H), 2.02 - 1.99 (m, 4H), 1.96 - 1.85 (m, 6H), 1.77 - 1.70 (m, 2H).

Example 84



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **84-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **84**. MS m/z = 818.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) *δ* ppm 8.49 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.82 - 4.79 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 8.0 Hz, 1H), 4.17 - 4.03 (m, 3H), 3.97 (s, 3H), 3.58 - 3.52 (m, 3H), 3.46 - 3.41 (m, 1H), 3.27 - 3.19 (m, 1H), 3.10 - 2.96 (m, 2H), 2.90 - 2.74 (m, 2H), 2.28-2.13 (m, 2H), 2.11-1.98 (m, 6H), 1.97-1.91 (m, 3H), 1.87-1.68 (m, 4H).

Example 86



Step 1

To a solution of compound **4-2** (100 mg, 113.64 μmol) in DCM (1 mL) was added TFA (0.2 mL), the mixture was stirred at 25 °C for 1 hour. The residue was redissolved in DCM (5 mL), washed with saturated $NaHCO_3$ solution (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **86-1**. MS m/z = 540.4 $[M+H]^+$.

Step 2

To a stirred solution of compound **86-2** (1 g, 4.15 mmol) in dry THF (15 mL) was added lithium bis(trimethylsilyl)amide (8.3 ml, 8.30 mmol, 1 M in THF) at -70 °C and the mixture was stirred at -70 °C for 0.5 hours. Then 1-chloro-3-iodopropane (1.27 g, 6.22 mmol) was added at -70 °C, and the reaction was stirred at -70 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution

(10 mL), extracted wtih EtOAc (3 × 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **86-3**. MS m/z =318.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **86-3** (40 mg, 126.18 μmol) in DCM (8 mL) was added 3-chloroperoxybenzoic acid (43.40 mg, 252.36 μmol) and the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 30:1) to afford compound **86-4A** (PE:EtOAc = 10:1, Rf = 0.45; MS m/z = 334.3 $[M+H]^+$) and compound **86-4B** (PE:EtOAc = 10:1, Rf = 0.4; MS m/z = 334.3 $[M+H]^+$).

Step 4

To a stirred solution of compound **86-4B** (1 g, 3.00 mmol) in MeOH (20 mL) was added iodotrimethylsilane (899.14 mg, 4.49 mmol) at 0 °C and the mixture was stirred at 50 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 1:10) to afford compound **86-5B**. MS m/z = 326.1 $[M+H]^+$.

Step 5

To a stirred solution of compound **86-5B** (100 mg, 429.18 μmol) in acetonitrile (3 mL) was added potassium carbonate (118.4 mg, 858.36 μmol) and the mixture was stirred at 60 °C for 4 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **86-6B**. MS m/z = 198.2 $[M+H]^+$.

Step 6

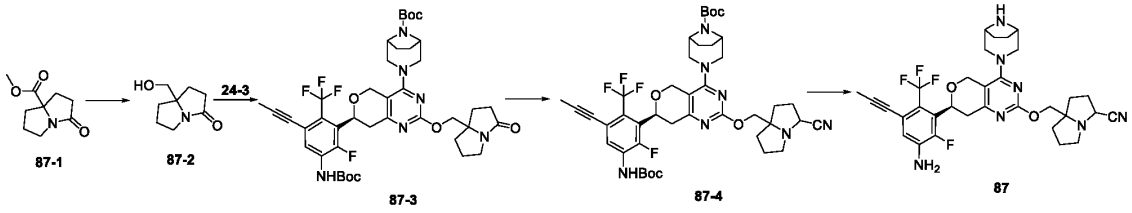
To a stirred solution of compound **86-6B** (100 mg, 0.51 mmol) in dry THF (3 mL) was added lithium aluminum hydride (0.41 ml, 1.02 mmol, 2.5 M in THF) at -40 °C under nitrogen atmosphere. The reaction was stirred at -40 °C for 15 minutes. The reaction was diluted with DCM (5 mL), quenched with water (0.2 mL), 15% NaOH solution (0.2 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 10 minutes. The reaction was filtered, the filter was washed with DCM (10 mL), the filtrate was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **86-7B**. MS m/z = 170.1 $[M+H]^+$.

Step 7

To a stirred solution of compound **86-7B** (30 mg, 176.47 μmol) in dry THF (1 mL) was added sodium hydride (10 mg, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **86-1** (95 mg, 176.47 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (5 × 6 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under

reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 45%-70%) to afford compound **86**. MS m/z = 629.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.29 - 4.26 (m, 1H), 4.24 - 4.10 (m, 2H), 3.52 - 3.48 (m, 2H), 3.47 - 3.38 (m, 1H), 3.27 - 3.18 (m, 1H), 3.18 - 3.08 (m, 2H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.94 (d, *J* = 12.0 Hz, 1H), 2.91 - 2.79 (m, 3H), 2.77 - 2.71 (m, 1H), 2.23 - 2.19 (m, 1H), 2.17 - 2.07 (m, 1H), 2.04 - 1.99 (m, 6H), 1.97 - 1.75 (m, 5H), 1.74 - 1.59 (m, 1H).

Example 87



Step 1

To a stirred solution of compound **87-1** (800 mg, 4.37 mmol) in dry THF (10 mL) was added lithium borohydride (190.25 mg, 8.73 mmol) at 0 °C. The mixture was stirred at 25 °C for 4 hours. The reaction was quenched with water (8 mL), The reaction was filtered, the filter was washed with acetonitrile (20 mL), the filtrate was concentrated under reduced pressure to afford compound **87-2**. MS m/z = 156.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **87-2** (150 mg, 966.53 μmol) in dry THF (8 mL) was added sodium hydride (46.39 mg，1.93 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **24-3** (489.69 mg, 676.57 μmol) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (4 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **87-3**. MS m/z = 815.6 $[M+H]^+$.

Step 3

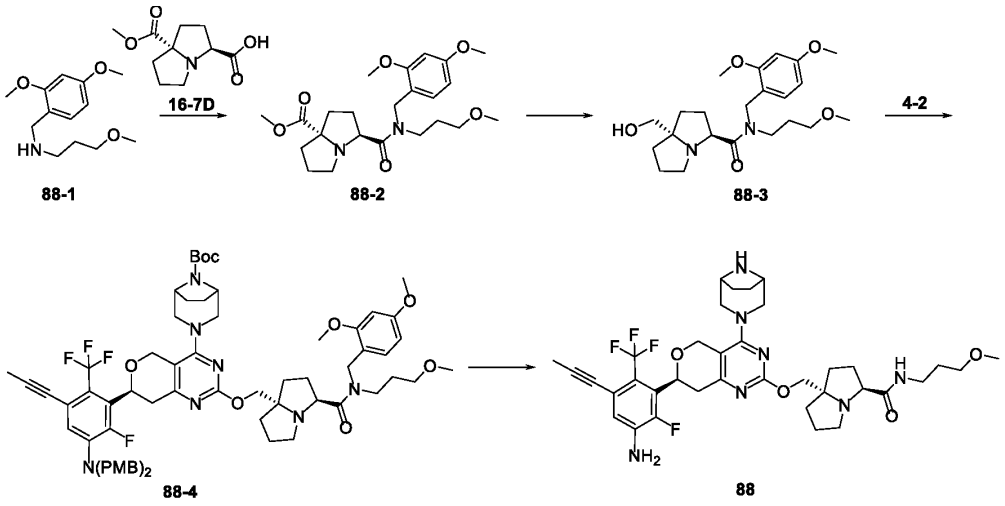
To a stirred solution of compound **87-3** (500 mg, 613.60 μmol) in dry THF (10 mL) was added LDBIPA (lithium diisobutyl-iso-propoxyaluminum hydride) (10 mL, 0.44 M in THF) at 0 °C and the mixture was stirred at 25 °C for 8 hours. The reaction was monitored by TLC (PE:EtOAc = 1:1) to found the start material was fully consumed. Then trimethylsilyl cyanide (304.36 mg, 3.07 mmol) was added, and the reaction was stirred at 25 °C for 4 hours. The reaction was quenched with water

(10 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **87-4**. MS m/z = 826.6 $[M+H]^+$.

Step 4

To a stirred solution of compound **87-4** (80 mg, 96.87 μmol) in MeOH (3 mL) was added iodotrimethylsilane (96.91 mg, 484.33 μmol) and the mixture was stirred at 50 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 45%-85%) to afford compound **87**. MS m/z = 626.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.68 - 4.62 (m, 1H), 4.16 - 4.09 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.61 - 3.51 (m, 3H), 3.46 - 3.39 (m, 1H), 3.24 - 3.16 (m, 1H), 3.09 - 3.02 (m, 2H), 2.87 - 2.80 (m, 1H), 2.43 - 1.93 (m, 11H), 1.91 - 1.79 (m, 4H), 1.75 - 1.67 (m, 2H).

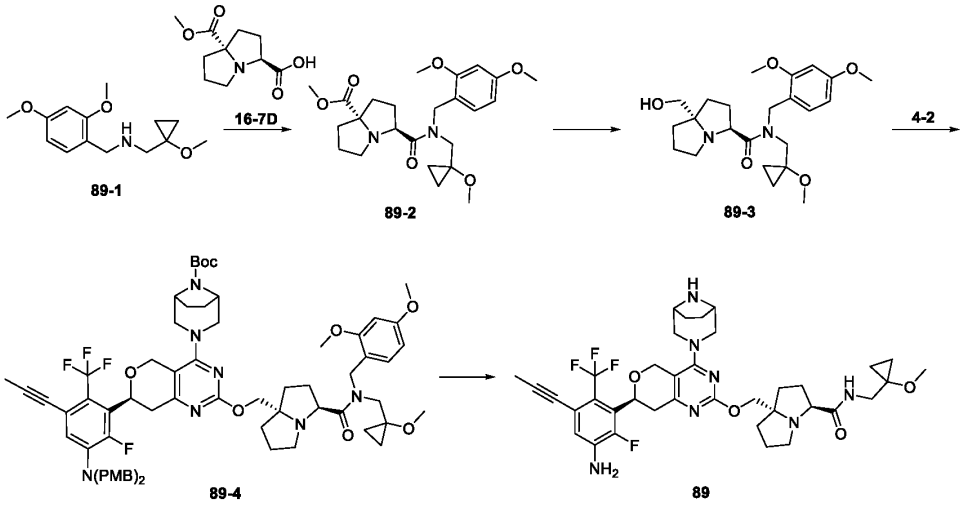
Example 88



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **88-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **88**. MS m/z = 716.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.17 (t, *J* = 12.0 Hz, 2H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.79 - 3.76 (m, 1H), 3.63 (s, 2H), 3.56 (d, *J* = 12.0 Hz, 1H), 3.46 - 3.43 (m, 3H), 3.36 - 3.32 (m, 4H), 3.28 - 3.25 (m,

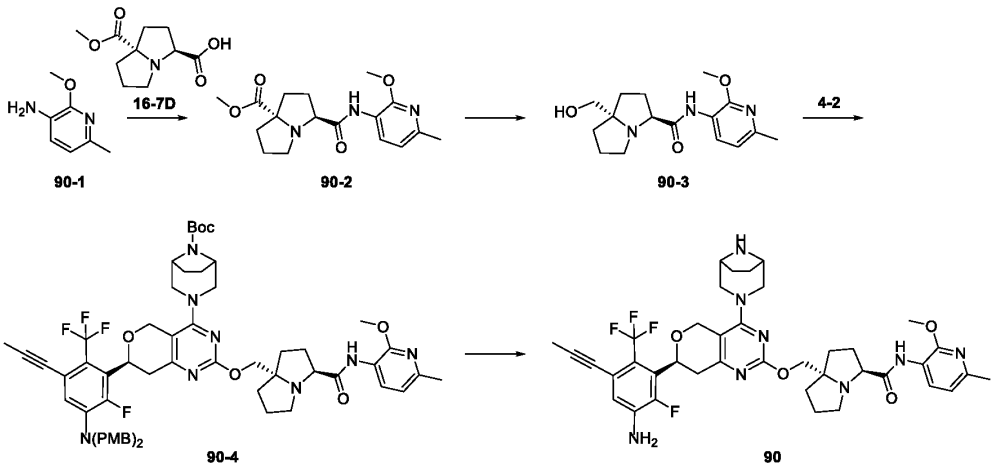
1H), 3.24 - 3.19 (m, 1H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.93 (m, 1H), 2.85 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.80 - 2.74 (m, 1H), 2.14 - 2.08 (m, 2H), 2.05 - 1.99 (m, 5H), 1.96 - 1.86 (m, 6H), 1.81 - 1.71 (m, 4H).

Example 89



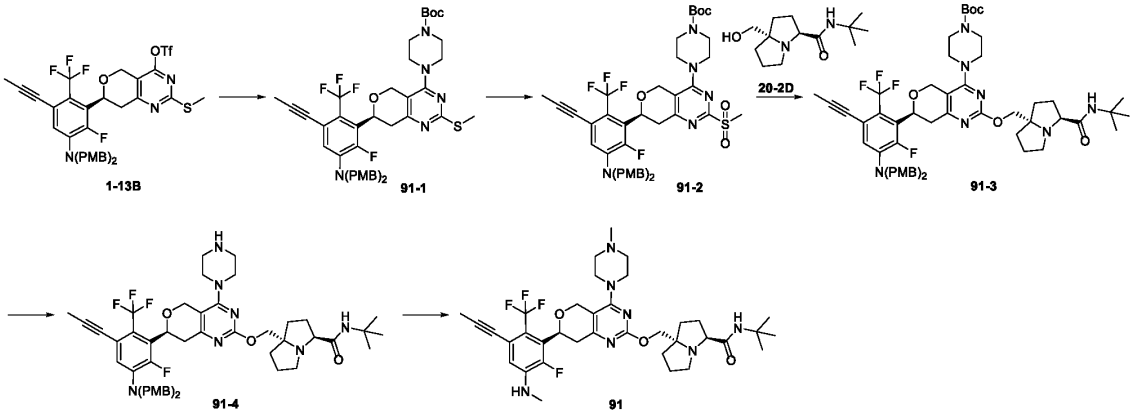
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **89-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **89**. MS m/z = 728.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.05 (t, *J* = 4.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H), 5.02 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 3.92 (t, *J* = 12.0 Hz, 2H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.60 (t, *J* = 4.0 Hz, 1H), 3.42 - 3.37 (m, 3H), 3.25 - 3.20 (m, 2H), 3.19 (s, 3H), 3.03 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.86 (d, *J* = 12.0 Hz, 1H), 2.80 - 2.72 (m, 2H), 2.67 - 2.63 (m, 1H), 2.03 (s, 3H), 2.01 - 1.94 (m, 1H), 1.93 - 1.71 (m, 8H), 1.65 - 1.48 (m, 4H), 0.68 - 0.58 (m, 2H), 0.56 - 0.48 (m, 2H).

Example 90



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **90-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-90%) to afford compound **90**. MS m/z = 765.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 4.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 4.03 - 3.99 (m, 1H), 3.98 (s, 3H), 3.54 (d, *J* = 8.0 Hz, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.23 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.08 - 2.96 (m, 2H), 2.86 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.81 - 2.74 (m, 1H), 2.39 (s, 3H), 2.23 - 2.11 (m, 2H), 2.08 - 1.99 (m, 5H), 1.98 - 1.87 (m, 4H), 1.86 - 1.65 (m, 4H).

Example 91



Step 1

To a stirred solution of compound **1-13B** (300 mg, 381.80 μmol) in N,N-dimethylformamide (10 mL) was added N,N-diisopropylethylamine (148.04 mg, 1.15 mmol) and 1-Boc-piperazine (142.22

mg, 763.60 μmol). The resulting mixture was stirred at 50 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **91-1**. MS m/z = 822.6 $[M+H]^+$.

Step 2

To a stirred solution of compound **91-1** (130 mg, 158.17 μmol) in DCM (10 mL) was added 3-chloroperoxybenzoic acid (68.24 mg, 395.42 μmol) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **91-2**. MS m/z = ,854.6$[M+H]^+$.

Step 3

To a stirred solution of compound **20-2D** (28.15 mg, 117.11 μmol) in dry THF (3 mL) was added sodium hydride (14.05 mg, 351.32 μmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours. Then compound **91-2** (100 mg, 117.11 μmol was added and the resulting mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **91-3**. MS m/z = 1014.8 $[M+H]^+$.

Step 4

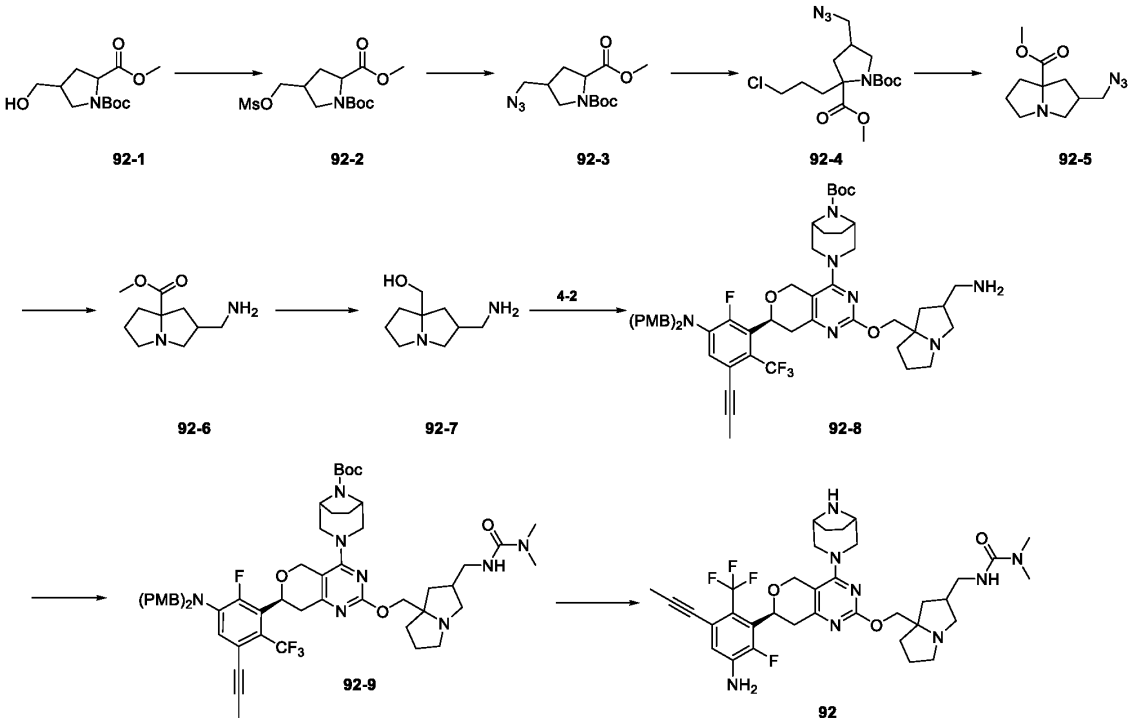
To a stirred solution of compound **91-3** (100 mg, 98.6 μmol) in DCM (10 mL) was added zinc bromide (66.6 mg, 295.8 μmol) and the mixture was stirred at 25 °C for 4 hours. The reaction was filtered, the filter was washed with DCM (20 mL), the filtrate was concentrated under reduced pressure to afford crude compound **91-4**. MS m/z = 914.7 $[M+H]^+$.

Step 5

To a stirred solution of compound **91-4** (30.00 mg, crude) in MeOH (3 mL) was added paraformaldehyde (3.00 mg, 98.46 μmol) and acetic acid (187.6 μL, 3.28 μmol). The mixture was stirred at 25 °C for 2 hours. Then sodium cyanoborohydride (4.13 mg, 65.64 μmol) was added and the resulting mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **91**. MS m/z = 702.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.74 (d, *J* = 12.0 Hz, 1H), 5.17 (dd, *J* =

12.0, 4.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.18 (d, *J* = 8.0 Hz, 1H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.61 - 3.53 (m, 2H), 3.48 - 3.40 (m, 2H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.95 - 2.84 (m, 5H), 2.78 - 2.71 (m, 1H), 2.64 - 2.58 (m, 2H), 2.54 - 2.49 (m, 2H), 2.34 (s, 3H), 2.14 - 2.06 (m, 2H), 2.04 (s, 3H), 1.94 - 1.83 (m, 5H), 1.74 - 1.69 (m, 1H), 1.35 (s, 9H).

Example 92



Step 1

To a stirred solution of compound **92-1** (600 mg, 2.31 mmol) in DCM (6 mL) was added triethyl amine (351.22 mg, 3.47 mmol) and methanesulfonyl chloride (530.13 mg, 4.63 mmol). The mixture was stirred at 25 °C for 4 hours. The reaction was quenched with water (20 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **92-2**. MS m/z =238.0 $[M+H-Boc]^+$.

Step 2

To a stirred solution of compound **92-2** (500 mg, 1.48 mmol) in N,N-dimethylformamide (5 mL) was added sodium azide (289.03 mg, 4.45 mmol) and the mixture was stirred at 80 °C for 4 hours. The reaction was quenched with water (15 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the

filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 1:1) to afford compound **92-3**. MS m/z =185.1 $[M+H\text{-}Boc]^+$.

Step 3

To a stirred solution of compound **92-3** (210 mg, 738.63 μmol) in dry THF (3 mL) was added lithium bis(trimethylsilyl)amide (247.18 mg, 1.48 mmol, 1 M in THF) at -78 °C and the mixture was stirred at -78 °C for 0.5 hours under nitrogen atmosphere. Then 1-chloro-3-iodopropane (226.50 mg, 1.11 mmol) was added at -78 °C, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **92-4**. MS m/z = 260.9 $[M+H\text{-}Boc]^+$.

Step 4

To a stirred solution of compound **92-4** (800 mg, 1.83 mmol) in DCM (10 mL) was added zinc bromide (1.24 g, 5.50 mmol) and the mixture was stirred at 25 °C for 16 hours. The reaction was diluted with water (20 mL), extracted wtih DCM (3 × 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **92-5**. MS m/z = 225.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **92-5** (60 mg, 267.55 μmol) in THF (2 mL) was added Pd/C (10 mg, 10% purity) and the mixture was stirred at 20 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **92-6**.MS m/z = 199.1 $[M+H]^+$.

Step 6

To a stirred solution of compound **92-6** (200 mg, 1.00 mmol) in dry THF (5 mL) was added lithium aluminum hydride (94.8 mg, 1.03 mmol) at 0 °C. The reaction was stirred at 0 °C for 0.3 hours. The reaction was quenched with sodium sulfate decahydrate, filtered, the filtrate was concentrated under reduced pressure to afford crude compound **92-7**. MS m/z = 171.1 $[M+H]^+$.

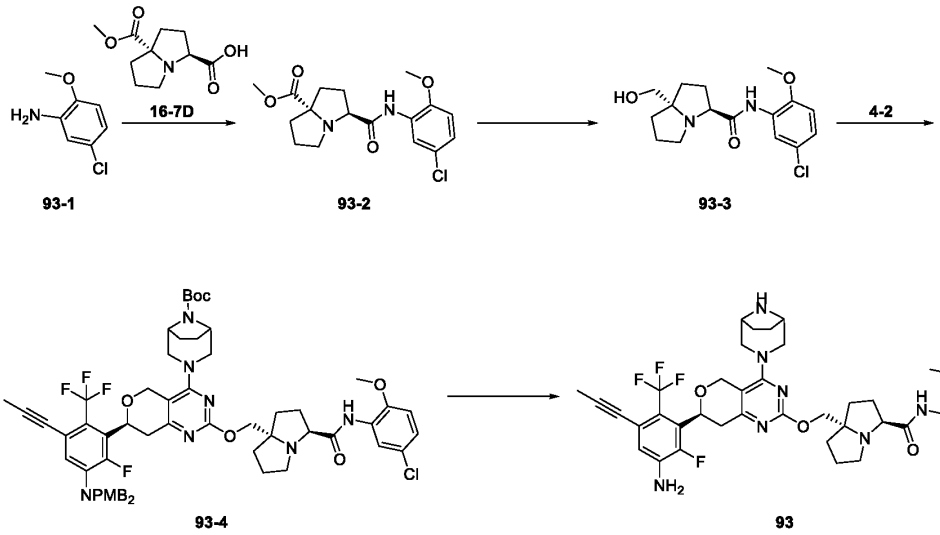
Step 7

To a stirred solution of compound **92-7** (8.71 mg, 51.14 μmol) in dry THF (1 mL) was added sodium hydride (1.23 mg, 51.14 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 30 minutes. Then compound **4-2** (30 mg, 34.09 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 15:1) to afford compound **92-8**. MS m/z = 970.7 $[M+H]^+$.

Step 8

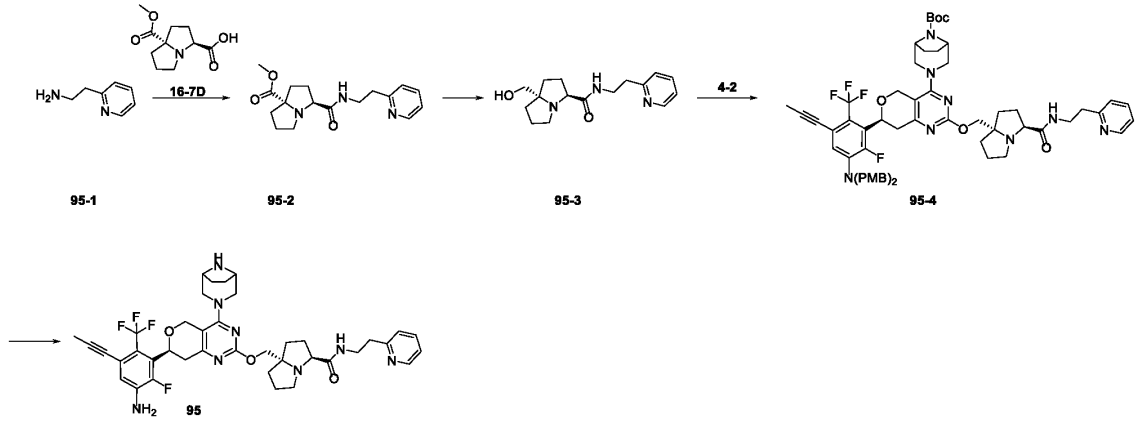
With reference to steps 7~8 of **Example 39**, compound **39-6B** was replaced with compound **92-8** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-90%) to afford compound **92**. MS m/z = 701.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 - 5.12 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.20 - 4.05 (m, 3H), 3.57 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.28 - 3.16 (m, 4H), 3.08 - 2.99 (m, 2H), 2.88 (s, 6H), 2.85 - 2.78 (m, 2H), 2.59 - 2.51 (m, 1H), 2.40 (t, *J* = 8.0 Hz, 1H), 2.33 - 2.21 (m, 1H), 2.04 - 2.00 (m, 4H), 1.99 - 1.87 (m, 3H), 1.86 - 1.80 (m, 3H), 1.72 - 1.60 (m, 1H), 1.41 (t, *J* = 12.0 Hz, 1H).

Example 93



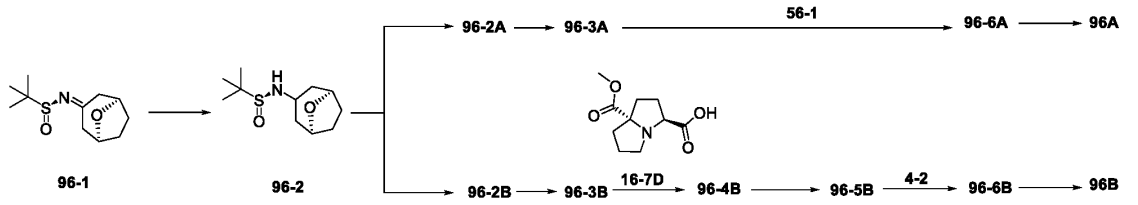
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **93-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 10%-40%) to afford compound **93**. MS m/z = 784.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm δ 8.17 (d, *J* = 4.0 Hz, 1H), 7.08 (dd, *J* = 12.0, 4.0 Hz, 1H), 7.00 (d, *J* = 12.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.09 (m, 2H), 4.02 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.89 (s, 3H), 3.57 - 3.51 (m, 3H), 3.45 - 3.40 (m, 1H), 3.26 - 3.19 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.01 - 2.96 (m, 1H), 2.86 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.80 - 2.73 (m, 1H), 2.17 - 2.12 (m, 1H), 2.07 - 2.03 (m, 2H), 2.02 (s, 3H), 1.96 - 1.88 (m, 4H), 1.86 - 1.80 (m, 2H), 1.78 - 1.69 (m, 2H), 1.62 - 1.58 (m, 1H).

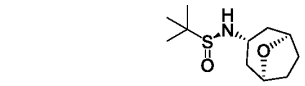
Example 95



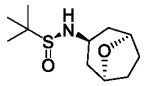
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **95-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **95**. MS m/z = 749.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 - 8.43 (m, 1H), 7.81 - 7.71 (m, 1H), 7.38 - 7.32 (m, 1H), 7.30 - 7.23 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.08 (m, 2H), 4.02 (d, *J* = 8.0Hz, 1H), 3.72 - 3.67 (m, 1H), 3.65 - 3.56 (m, 2H), 3.55 - 3.47 (m, 3H), 3.44 - 3.37 (m, 1H), 3.25 - 3.16 (m, 1H), 3.06 - 2.96 (m, 3H), 2.88 - 2.77 (m, 2H), 2.67 - 2.59 (m, 1H), 2.12 - 1.94 (m, 7H), 1.94 - 1.77 (m, 6H), 1.75 - 1.63 (m, 2H).

Example 96

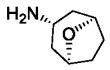




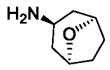
96-2A or 96-2B



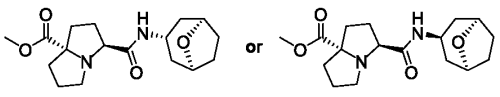
96-2B or 96-2A



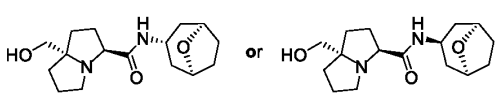
96-3A or 96-3B



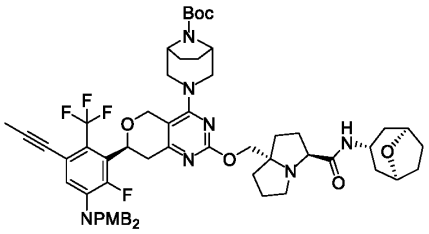
96-3B or 96-3A



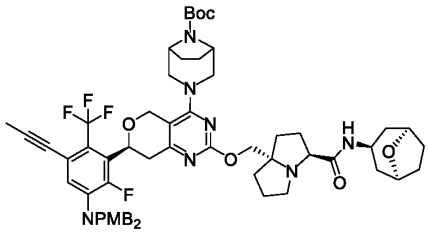
96-4B



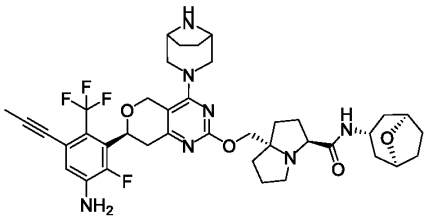
96-5B



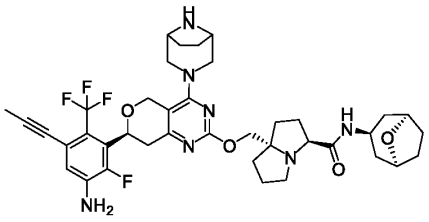
96-6A or 96-6B



96-6B or 96-6A



96A or 96B



96B or 96A

Step 1

To a stirred solution of compound **96-1** (3 g, 13.08 mmol) in MeOH (30 mL) was added sodium borohydride (1.48 g, 39.24 mmol). The mixture was stirred at 25 °C for 15 minutes. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 10:1) to afford compound **96-2**. MS m/z = 232.2 $[M+H]^+$. The compound **96-2** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®IC-10, 250*40mm 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: (0.05% NH_3/MeOH - MeOH); Gradient: B% 5%- 40%) to afford compound **96-2A** and compound **96-2B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®IC-3 (100*3mm 3μm); Mobile phase: A: Supercritical CO_2; B: (MeOH (0.05% - DEA); Gradient: B% 5%-40%, 4 min). Compound **96-2A**, Rt = 2.817 mins, ee: 100%, MS m/z = 232.2 $[M+H]^+$; compound **96-2B**, Rt = 3.662 mins, ee : 98.78%, MS m/z = 232.2 $[M+H]^+$.

Step 2

A solution of compound **96-2A** (300 mg, 1.30 mmol) in HCl (10 mL, 4 M in dioxane) was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford compound **96-**

3A as HCl salt, the crude product was used in the next step directly. MS m/z = 128.1 $[M+H]^+$.

With reference to step 2, compound **96-2A** was replaced with compound **96-2B** as the raw material to obtain compound **96-3B**. MS m/z = 128.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **56-1** (60 mg, 60.91 μmol) in DCM (2 mL) was added N,N-diisopropylethylamine (39.36 mg, 304.55 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (39.37 mg, 103.55 μmol) and compound **96-3A** (11.62 mg, 91.36 μmol). The resulting mixture was stirred at 25 °C for 3 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **96-6A**. MS m/z = 1094.7 $[M+H]^+$.

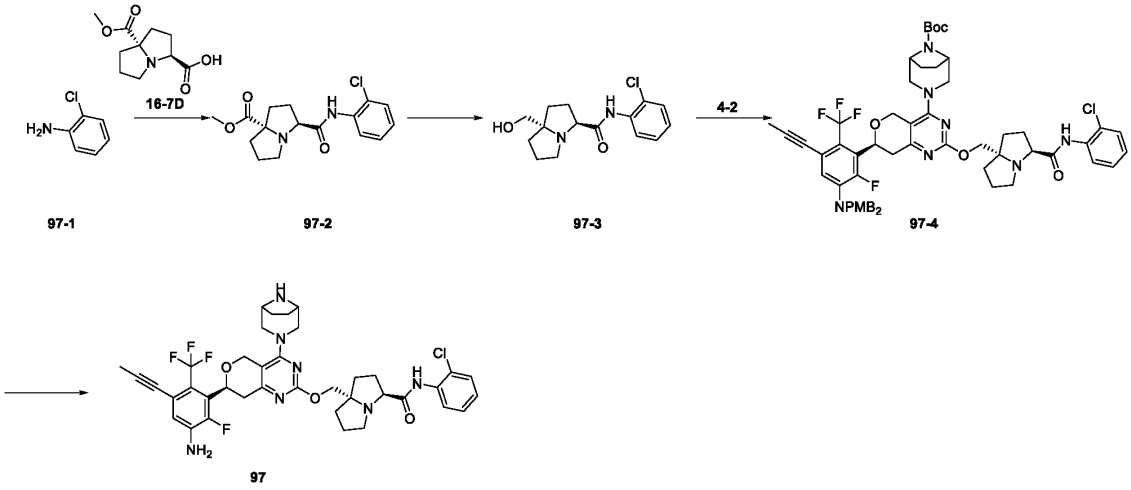
Step 4

To a solution of compound**96-6A** (20 mg, 18.28 μmol) in DCM (0.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **96A**. MS m/z = 754.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, J = 8.0 Hz, 1H), 5.14 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 - 4.79 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.40 (s, 2H), 4.24 - 4.12 (m, 3H), 4.04 (d, J = 12.0 Hz, 1H), 3.72 (dd, J = 8.0, 4.0 Hz, 1H), 3.57 - 3.50 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.92 - 2.80 (m, 2H), 2.77 - 2.70 (m, 1H), 2.11 - 2.06 (m, 2H), 2.03 - 1.99 (m, 4H), 1.98 - 1.67 (m, 15H), 1.62 - 1.56 (m, 2H).

Step 5

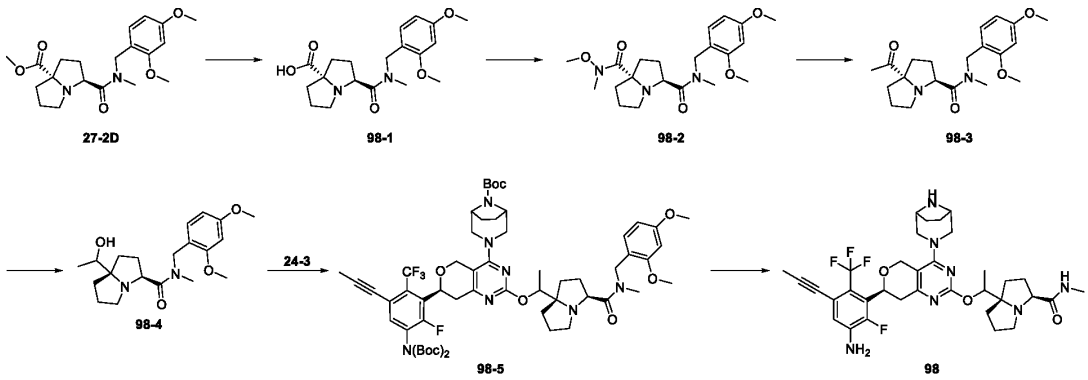
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **96-3B** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **96**. MS m/z = 754.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.34 (s, 2H), 4.20 - 4.13 (m, 2H), 4.09 (d, J = 12.0 Hz, 1H), 3.98 (t, J = 8.0 Hz, 1H), 3.80 - 3.76 (m, 1H), 3.61 - 3.51 (m, 3H), 3.44 (d, J = 12.0 Hz, 1H), 3.26 - 3.18 (m, 1H), 3.06 (d, J = 12.0 Hz, 1H), 2.96 - 2.82 (m, 2H), 2.75 - 2.66 (m, 1H), 2.23 - 2.08 (m, 7H), 2.04 - 1.99 (m, 5H), 1.98 - 1.86 (m, 8H), 1.74 - 1.69 (m, 3H).

Example 97



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **97-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **97**. MS m/z = 754.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.84 - 7.82 (m, 1H), 7.47 - 7.45 (m, 1H), 7.31 (td, *J* = 8.0, 4.0 Hz, 1H), 7.19 (td, *J* = 8.0, 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.09 (m, 2H), 4.06 - 4.02 (m, 1H), 3.60 - 3.51 (m, 3H), 3.47 - 3.40 (m, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.12 - 3.00 (m, 2H), 2.91 - 2.75 (m, 2H), 2.30 - 2.06 (m, 4H), 2.02 (s, 3H), 2.00 - 1.91 (m, 4H), 1.88 - 1.67 (m, 4H).

Example 98



Step 1

To a stirred solution of compound **27-2D** (400 mg, 1.06 mmol) in THF (3 mL) and water (3 mL) was added lithium hydroxide monohydrate (89.36 mg, 2.12 mmol) and the mixture was stirred at 50 °C for 4 hours. The reaction was cooled down to room tempetature and extracted wtih EtOAc (3

× 6 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **98-1**. MS m/z = 361.2 $[M-H]^-$.

Step 2

To a stirred solution of compound **98-1** (300 mg，829 μmol) in DCM (10 mL) was added N,N-diisopropylethylamine (320.72 mg, 2.49 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (377.9 mg, 994.8 μmol). The mixture was stirred at 25 °C for 0.5 hours. Then N,O-dimethylhydroxylamine hydrochloride (96.96 mg, 994.8 mmol) was added and the resulting mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **98-2**. MS m/z = 406.3 $[M+H]^+$.

Step 3

To a stirred solution of compound **98-2** (150.00 mg, 370.16 μmol) in dry THF (5 mL) was added methylmagnesium bromide (0.30 mL, 296.13 μmol, 1 M in THF) at -78 °C under nitrogen atmosphere and the mixture was stirred at -78 °C for 2 hours. The reaction was quenched with water (4 mL), filtered, the filter was washed with acetonitrile (10 mL), the filtrate was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (ACN-H_2O (0.1% FA); Gradient: (ACN): 0%-30%) to afford compound **98-3**. MS m/z = 361.3 $[M+H]^+$.

Step 4

To a stirred solution of compound **98-3** (90 mg, 249.86 μmol) in MeOH (2 mL) was added sodium borohydride (47.26 mg, 1.25 mmol) portionwise at 0 °C. The mixture was stirred at 25 °C for 8 hours. The reaction was quenched with water (2 mL), filtered, the filter was washed with acetonitrile (10 mL), the filtrate was concentrated under reduced pressure to afford crude compound **98-4**. MS m/z = 363.3 $[M+H]^+$.

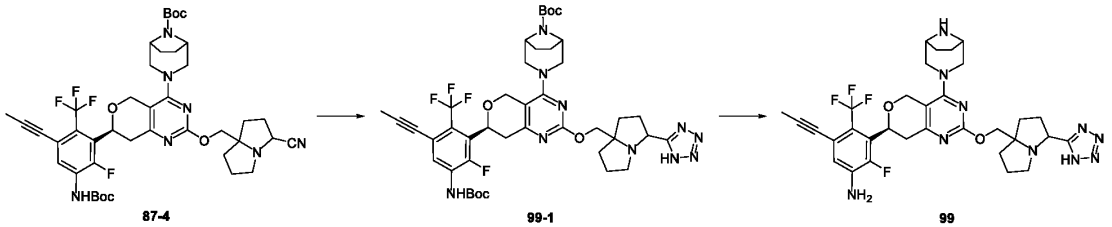
Step 5

To a stirred solution of compound **98-4** (50 mg, crude) in dry THF (5 mL) was added sodium hydride (11.05 mg, 0.28 mmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **24-3** (94.92 mg, 110.48 μmol) was added, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (3 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **98-5**. MS m/z = 1022.8 $[M-Boc+H]^+$.

Step 6

To a solution of compound **98-5** (60 mg, 53.50 μmol) in DCM (1.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-85%) to afford compound **98**. MS m/z = 672.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.12 (m, 1H), 4.78 (s, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.08 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.58 - 3.49 (m, 3H), 3.45 - 3.36 (m, 1H), 3.29 - 3.14 (m, 3H), 3.08 - 3.02 (m, 1H), 3.01 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.69 (s, 1H), 2.68 - 2.62 (m, 1H), 2.60 (s, 2H), 2.32 - 2.20 (m, 1H), 2.19 - 2.13 (m, 1H), 2.01 (s, 3H), 2.00 - 1.88 (m, 2H), 1.86 - 1.74 (m, 5H), 1.72 - 1.66 (m, 2H), 1.64 - 1.55 (m, 1H), 1.33 (t, *J* = 8.0 Hz, 3H).

Example 99



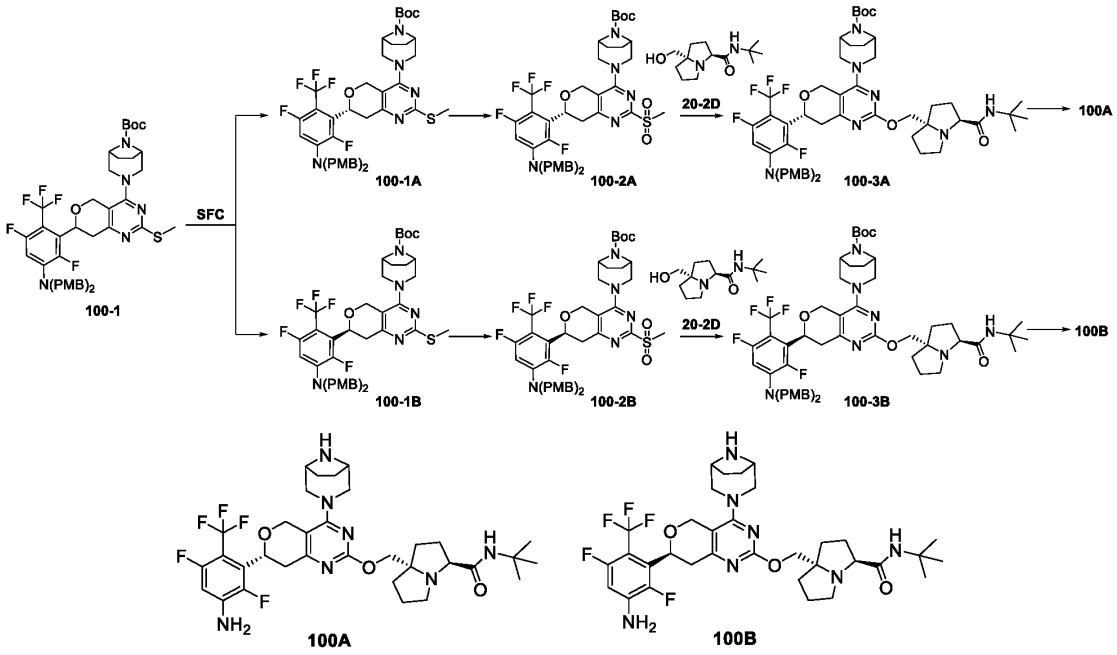
Step 1

To a stirred solution of compound **87-4** (100 mg, 121.08 μmol) in N,N-dimethylformamide (2 mL) was added sodium azide (78.72 mg, 1.21 mmol) and NH_4Cl (64.77 mg，1.21 mmol). The mixture was stirred at 70 °C for 48 hours. The reaction was quenched with water (6 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **99-1**. MS m/z = 869.7 $[M+H]^+$.

Step 2

To a solution of compound **99-1** (100 mg, 115.09 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 10%-50%) to afford compound **99**. MS m/z = 669.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (s, 1H), 4.67 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.44 - 4.36 (m, 2H), 4.23 - 4.17 (m, 2H), 3.89 (s, 2H), 3.66 (d, *J* = 16.0 Hz, 1H), 3.52 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.24 - 3.14 (m, 4H), 2.86 - 2.77 (m, 1H), 2.54 - 2.46 (m, 1H), 2.42 - 2.34 (m, 2H), 2.19 - 1.83 (m, 12H).

Example 100



Step 1

The compound **100-1** (390 mg, 471.41 μmol) was separated by preparative SFC (Column name: Regis (S,S)Whelk-O 1, 25*250 mm 10 mm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: IPA 50% + ACN 50% +(0.05%)(NH_3 in MeOH); Gradient: B% 50%) to afford compound **100-1A** and compound **100-1B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®WHELK-O1 (4.6 mm*150 mm,5 μm); Mobile phase: A: Supercritical CO_2; B: IPA 50% + ACN 50% +(0.05%)(NH_3 in MeOH); Gradient: B% 50%). Compound **100-1A**, Rt = 7.180 mins, MS m/z = 828.6 $[M+H]^+$; compound **100-1B**, Rt = 9.250 mins, MS m/z = 828.6 $[M+H]^+$.

Step 2

To a stirred solution of compound **100-1A** (170 mg, 205.49 μmol) in DCM (2 mL) was added 3-chloroperoxybenzoic acid (91.71 mg, 451.75 μmol, 85% purity) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated solution of sodium sulfite (5 mL), extracted wtih DCM (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **100-2A**. MS m/z = 860.5 $[M+H]^+$.

With reference to step 2, compound **100-1A** was replaced with compound **100-1B** as the raw material to obtain compound **100-2B**. MS m/z = 860.5 $[M+H]^+$.

Step 3

To a stirred solution of compound **20-2D** (39.97 mg, 166.30 μmol) in dry THF (2 mL) was added sodium hydride (9.07 mg, 226.77 μmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours. Then compound **100-2A** (130 mg, 151.18 μmol) was added and the resulting mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **100-3A**. MS m/z = 1020.7 $[M+H]^+$.

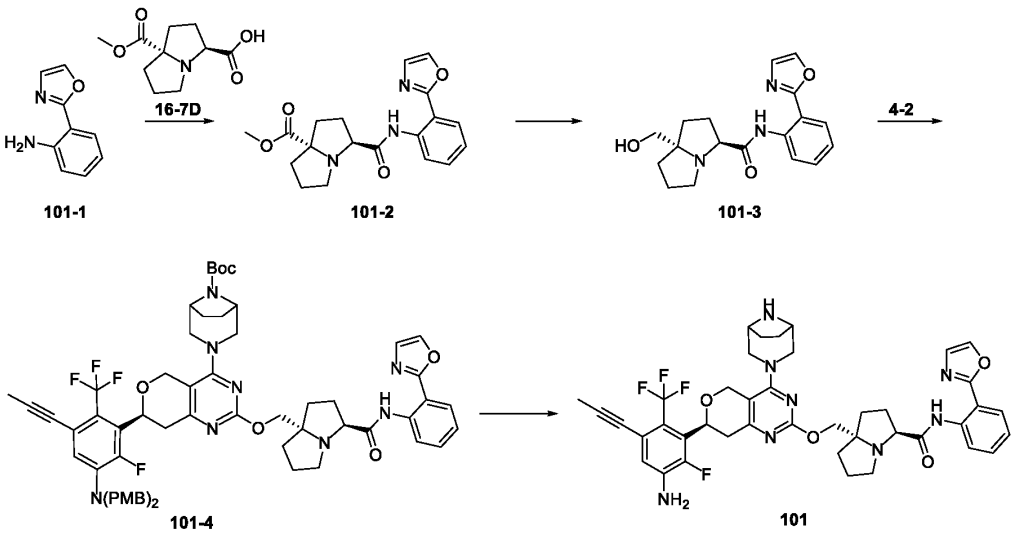
With reference to step 3, compound **100-2A** was replaced with compound **100-2B** as the raw material to obtain compound **100-3B**. MS m/z = 1020.7 $[M+H]^+$.

Step 4

To a solution of compound **100-3A** (95 mg, 93.13 μmol) in DCM (2 mL) was added TFA (0.4 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **100A**. MS m/z = 680.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.60 - 6.55 (m, 1H), 5.13 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.13 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.70 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.54 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.83 (m, 2H), 2.78 - 2.72 (m, 1H), 2.14 - 2.05 (m, 2H), 2.03 - 1.98 (m, 1H), 1.93 - 1.78 (m, 7H), 1.74 - 1.66 (m, 2H), 1.35 (s, 9H).

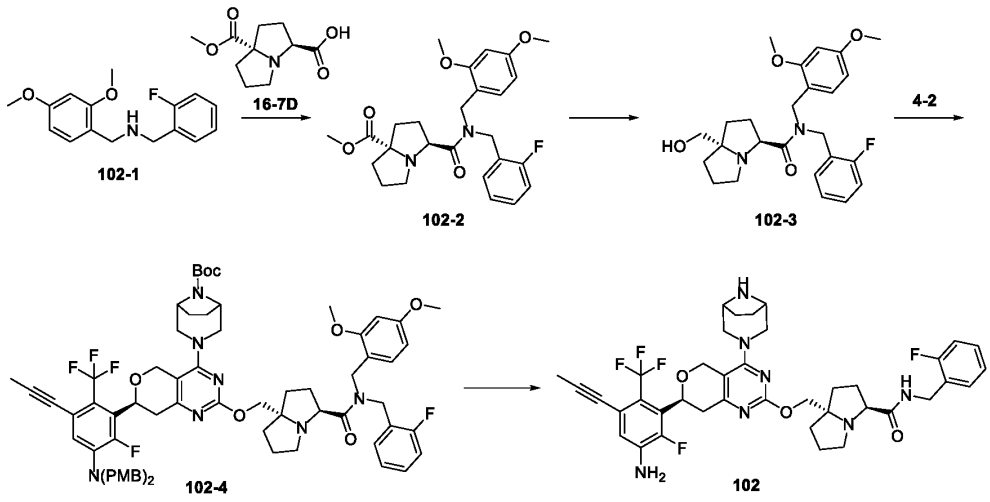
To a solution of compound **100-3B** (90 mg, 88.22 μmol) in DCM (2 mL) was added TFA (0.4 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **100B**. MS m/z = 680.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.61 - 6.56 (m, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.79 (s, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.70 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.54 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.83 (m, 2H), 2.78 - 2.72 (m, 1H), 2.14 - 2.05 (m, 2H), 2.01 (t, *J* = 8.0 Hz, 1H), 1.93 - 1.78 (m, 7H), 1.75 - 1.67 (m, 2H), 1.36 (s, 9H).

Example 101



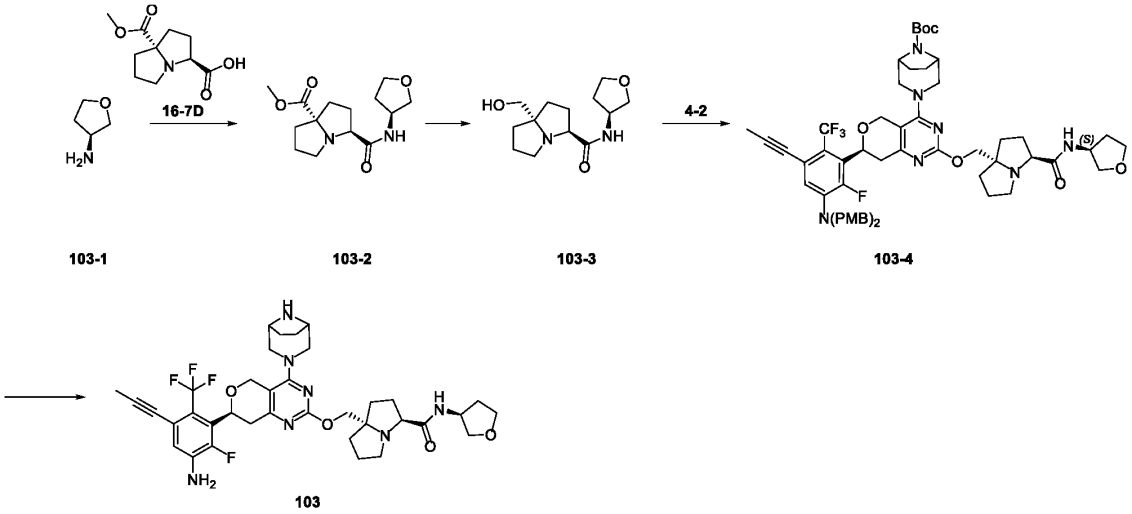
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **101-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 65%-70%) to afford compound **101**. MS m/z = 787.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.74 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0, 1H), 7.93 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.05 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.56 (d, *J* = 16.0 Hz, 1H), 4.30 - 4.23 (m, 2H), 3.91 (d, *J* = 12.0 Hz, 1H), 3.53 (t, *J* = 8.0 Hz, 1H), 3.41 - 3.32 (m, 4H), 3.22 - 3.17 (m, 1H), 3.12 - 3.03 (m, 1H), 2.82 (d, *J* = 12.0 Hz, 1H), 2.79 - 2.68 (m, 2H), 2.49 - 2.40 (m, 1H), 2.23 - 2.15 (m, 2H), 2.13 - 2.02 (m, 3H), 2.01 (s, 3H), 1.85 - 1.75 (m, 3H), 1.72 - 1.63 (m, 2H), 1.57 - 1.50 (m, 1H).

Example 102



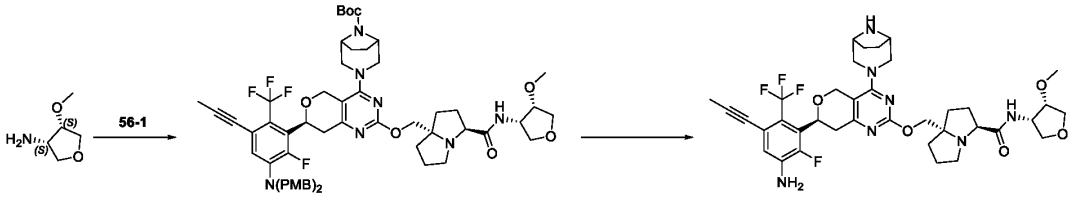
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **102-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 20%-50%) to afford compound **102**. MS m/z = 752.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.38 (t, *J* = 8.0 Hz, 1H), 7.33 - 7.27 (m, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.50 (d, *J* = 16.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.11 (m, 2H), 4.04 (d, *J* = 8.0 Hz, 1H), 3.79 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.53 - 3.50 (m, 3H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.20 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.03 (d, *J* = 16.0 Hz, 1H), 2.90 - 2.80 (m, 2H), 2.76 - 2.70 (m, 1H), 2.15 - 2.06 (m, 2H), 2.03 - 1.97 (m, 5H), 1.95 - 1.80 (m, 6H), 1.76 - 1.65 (m, 2H).

Example 103



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **103-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **103**. MS m/z = 714.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.42 - 4.37 (m, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.97 - 3.72 (m, 4H), 3.66 - 3.59 (m, 1H), 3.55 - 3.40 (m, 3H), 3.26 - 3.17 (m, 2H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.96 - 2.81 (m, 2H), 2.80 - 2.71 (m, 1H), 2.28 - 2.16 (m, 2H), 2.16 - 2.08 (m, 3H), 2.03 - 1.98 (m, 5H), 1.95 - 1.91 (m, 3H), 1.87 - 1.82 (m, 2H), 1.76 - 1.69 (m, 2H).

Example 104



104-1 104-2 104

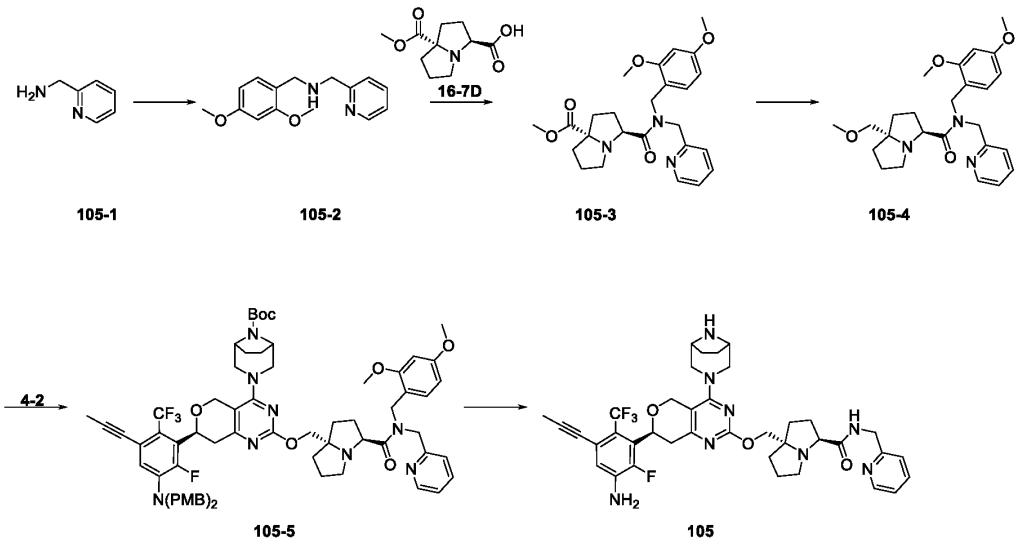
Step 1

To a stirred solution of compound **56-1** (60 mg, 60.91 μmol) in DCM (2 mL) was added N,N-diisopropylethylamine (39.36 mg, 304.55 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (39.37 mg, 103.55 μmol) and compound **104-1** (14.27 mg, 121.82 μmol). The mixture was stirred at 25 °C for 3 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **104-2**. MS m/z = 1084.7 $[M+H]^+$.

Step 2

To a solution of compound **104-2** (35 mg, 32.28 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **104**. MS m/z = 744.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 - 4.77 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.48 - 4.43 (m, 1H), 4.19 - 4.11 (m, 2H), 4.07 (d, J = 12.0 Hz, 1H), 4.00 - 3.96 (m, 2H), 3.93 - 3.90 (m, 1H), 3.89 - 3.82 (m, 2H), 3.60 - 3.51 (m, 4H), 3.46 - 3.40 (m, 1H), 3.37 (s, 3H), 3.25 - 3.18 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.93 - 2.81 (m, 2H), 2.74 - 2.67 (m, 1H), 2.16 - 2.09 (m, 2H), 2.04 - 1.99 (m, 5H), 1.95 - 1.81 (m, 6H), 1.77 - 1.67 (m, 2H).

Example 105



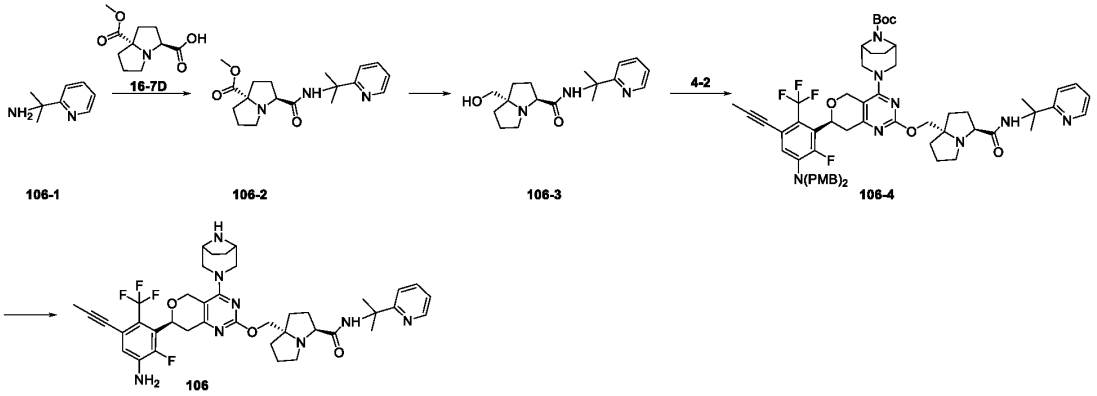
Step 1

To a stirred solution of compound **105-1** (500 mg, 4.62 mmol) in MeOH (5 mL) was added 2,4-dimethoxybenzaldehyde (768.32 mg, 4.62 mmol) and the mixture was stirred at 25 °C for 0.5 hours. Then sodium cyanoborohydride (581.11 mg, 9.25 mmol) was added and the resulting mixture was stirred at 25 °C for 15 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 15:1) to afford compound **105-2**. MS m/z = 259.17 $[M+H]^+$.

Step 2

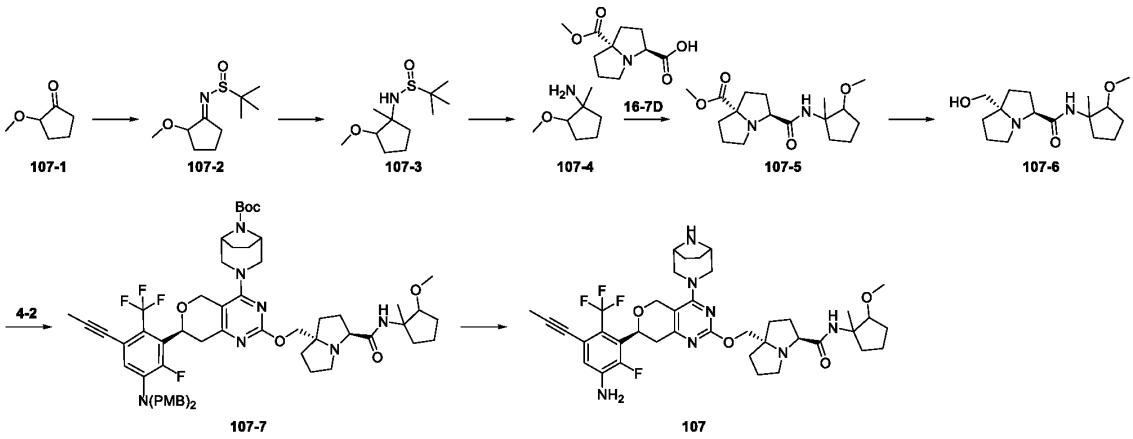
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **105-2** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **105**. MS m/z = 735.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.49 - 8.47 (m, 1H), 7.83 - 7.78 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.36 - 7.28 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.77 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.55 (s, 2H), 4.22 - 4.06 (m, 3H), 3.89 - 3.85 (m, 1H), 3.58 - 3.42 (m, 4H), 3.28 - 3.14 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.96 -2.91 (m, 1H), 2.87 - 2.73 (m, 2H), 2.20 - 2.06 (m, 3H), 2.03 (s, 3H), 2.01 - 1.66 (m, 9H).

Example 106



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **106-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **106**. MS m/z = 763.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 - 8.42 (m, 1H), 7.81 - 7.71 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.27 - 7.19 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.07 (d, *J* = 8.0 Hz, 1H), 3.87 - 3.81 (m, 1H), 3.58 - 3.49 (m, 3H), 3.45 - 3.38 (m, 1H), 3.27 - 3.18 (m, 1H), 3.07 - 3.01 (m, 1H), 3.01 - 2.95 (m, 1H), 2.89 - 2.81 (m, 1H), 2.77 - 2.69 (m, 1H), 2.14 - 1.98 (m, 6H), 1.97 - 1.80 (m, 7H), 1.76 - 1.63 (m, 8H).

Example 107



Step 1

To a stirred solution of compound **107-1** (2.2 g, 19.27 mmol) in dry THF (25 mL) was added titanium tetraisopropanolate (16.43 g, 57.82 mmol) and tert-butanesulfinamide (2.34 g, 19.27 mmol). The reaction was stirred at 25 °C for 3 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4.

After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **107-2**. MS m/z = 218.1 $[M+H]^+$.

Step 2

A solution of compound **107-2** (2.1 g, 9.66 mmol) and methylmagnesium bromide (15 mL, 1 M in THF) was stirred at 60 °C for 16 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **107-3**. MS m/z = 234.4 $[M+H]^+$.

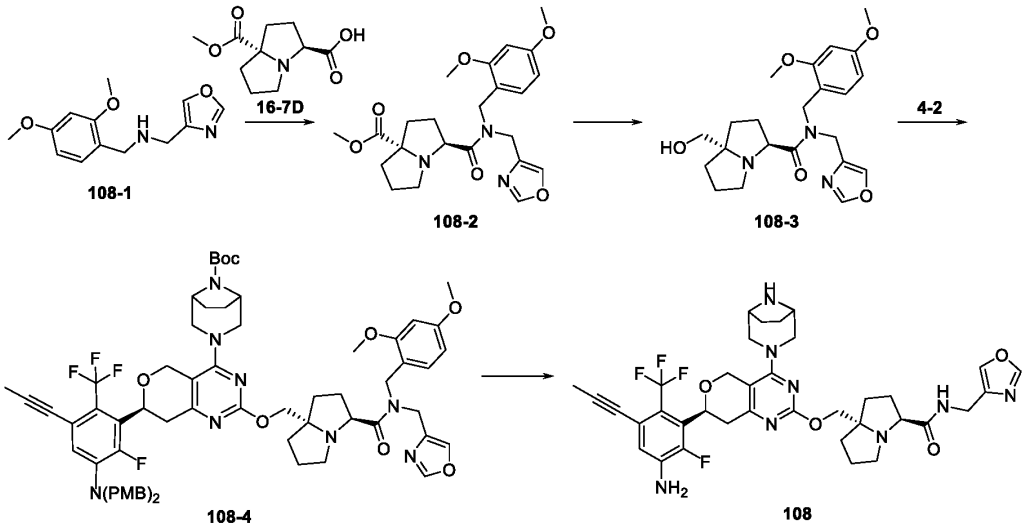
Step 3

A solution of compound **107-3** (340 mg, 1.46 mmol) in HCl (2 mL, 4 M in dioxane) was stirred at 25 °C for 3 hours. The reaction was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (ACN-H_2O (0.1% FA); Gradient: (ACN): 0%-20%) to afford compound **107-4**. MS m/z = 130.2 $[M+H]^+$.

Step 4

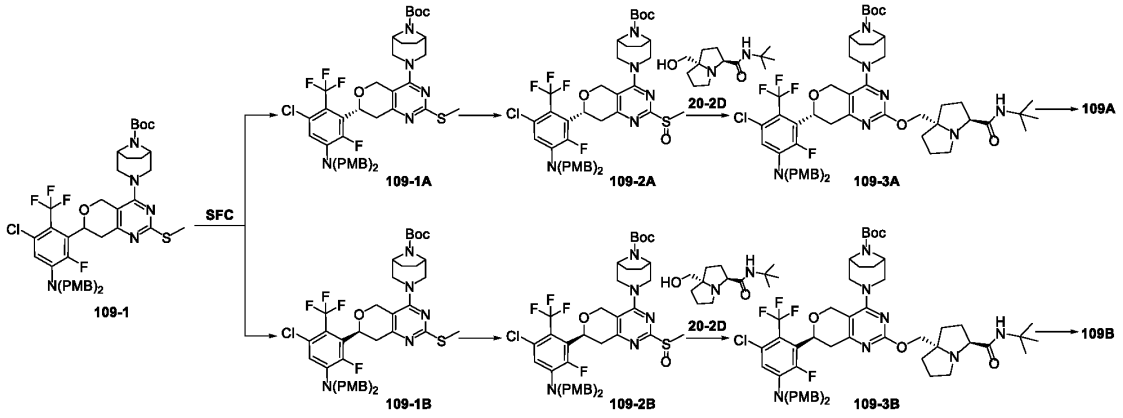
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **107-4** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: sunfire-C18, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 25%-60%) to afford compound **107** as FA salt. MS m/z = 756.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.47 (s, 1.82H), 6.88 (dd, *J* = 24.0, 8.0 Hz, 1H), 5.20 - 5.14 (m, 1H), 4.87 - 4.84 (m, 1H), 4.71 (d, *J* = 16.0 Hz,1H), 4.38 - 4.32 (m, 1H), 4.29 - 4.11 (m, 4H), 4.06 - 4.02 (m, 2H), 3.96 - 3.92 (m, 1H), 3.77 - 3.66 (m, 1H), 3.64 - 3.55 (m, 1H), 3.35 - 3.33 (m, 3H), 3.26 - 3.23 (m, 2H), 3.10 - 3.05 (m, 1H), 2.94 - 2.89 (m, 1H), 2.27 - 2.20 (m, 3H), 2.08 - 1.92 (m, 12H), 1.74 - 1.68 (m, 2H), 1.63 - 1.56 (m, 2H), 1.38 - 1.32 (m, 5H).

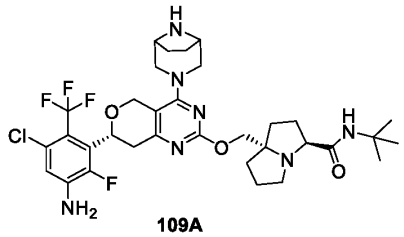
Example 108



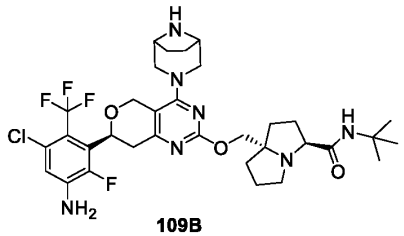
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **108-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **108**. MS m/z = 725.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.13 (s, 1H), 7.83 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.37 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 4.15 (t, *J* = 12.0 Hz, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.79 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.56 - 3.51 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.94 - 2.81 (m, 2H), 2.77 - 2.70 (m, 1H), 2.14 - 2.05 (m, 2H), 2.04 - 1.98 (m, 5H), 1.96 - 1.81 (m, 6H), 1.76 - 1.67 (m, 2H).

Example 109





109A



109B

Step 1

The compound **109-1** (500 mg, 592.90 μmol) was separated by preparative SFC (Column name: Regis (S,S)Whelk-O 1, 25*250 mm 10 mm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: IPA 50% + ACN 50% +(0.05%)(NH_3 in MeOH); Gradient: B% 50%) to afford compound **109-1A** and compound **109-1B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®WHELK-O1 (4.6 mm*150 mm,5 μm); Mobile phase: A: Supercritical CO_2; B: IPA 50% + ACN 50% +(0.05%)(NH_3 in MeOH); Gradient: B% 50%). Compound **109-1A**, Rt = 3.322 mins, MS m/z = 844.5 $[M+H]^+$; compound **109-1B**, Rt = 4.143 mins, MS m/z = 844.5 $[M+H]^+$.

Step 2

To a stirred solution of compound **109-1A** (210 mg, 249.02 μmol) in DCM (2 mL) was added 3-chloroperoxybenzoic acid (101.10 mg, 498.04 μmol, 85% purity) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated solution of sodium sulfite (5 mL), extracted wtih DCM (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **109-2A**. MS m/z = 860.5 $[M+H]^+$.

With reference to step 2, compound **109-1A** was replaced with compound **109-1B** as the raw material to obtain compound **109-2B**. MS m/z = 860.5 $[M+H]^+$.

Step 3

To a stirred solution of compound **20-2D** (35 mg, 145.63 μmol) in dry THF (3 mL) was added sodium hydride (5.82 mg, 145.63 μmol, 60% purity) and the mixture was stirred at 0 °C for 0.5 hours. Then compound **109-2A** (125.29 mg, 145.63 μmol) was added and the resulting mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **109-3A.** MS m/z = 1036.8 $[M+H]^+$.

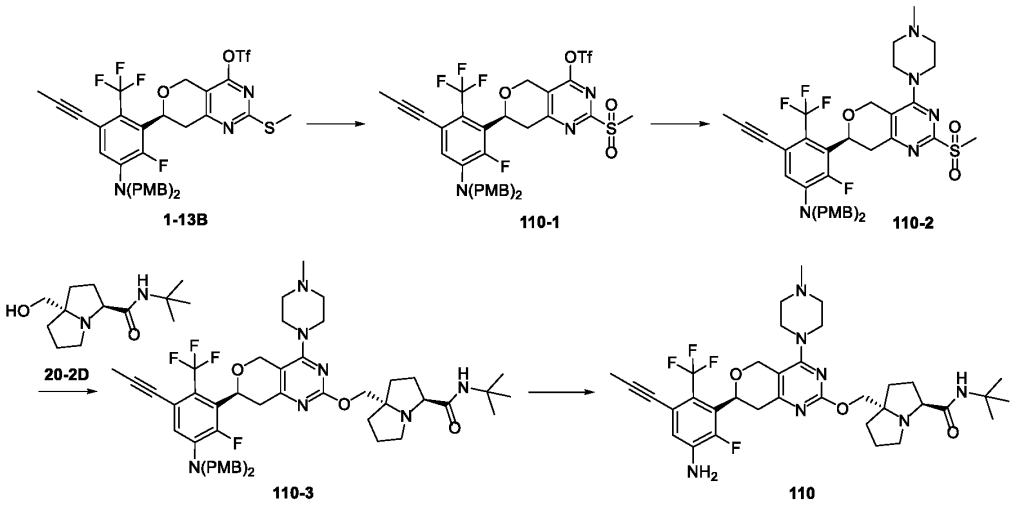
With reference to step 3, compound **109-2A** was replaced with compound **109-2B** as the raw material to obtain compound **109-3B**. MS m/z = 1036.8 $[M+H]^+$.

Step 4

To a solution of compound **109-3A** (100 mg, 96.47 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge C18 150*40mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **109A**. MS m/z = 696.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.21 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.70 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.53 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.95 - 2.85 (m, 2H), 2.78 - 2.72 (m, 1H), 2.14 - 1.98 (m, 3H), 1.92 - 1.81 (m, 7H), 1.74 - 1.66 (m, 2H), 1.36 (s, 9H).

To a solution of compound **109-3B** (90 mg, 88.22 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge C18 150*40mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-90%) to afford compound **109B**. MS m/z = 696.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.21 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.13 (m, 2H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.70 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.55 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.86 (m, 2H), 2.78 - 2.72 (m, 1H), 2.15 - 1.99 (m, 3H), 1.94 - 1.80 (m, 7H), 1.76 - 1.65 (m, 2H), 1.36 (s, 9H).

Example 110



Step 1

To a stirred solution of compound **1-13B** (200 mg, 254.53 μmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (129.19 mg, 636.34 μmol) and the mixture was stirred at 25 °C for 1 hour.

The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **110-1**. MS m/z = 818.4 $[M+H]^+$.

Step 2

To a stirred solution of compound **110-1** (200 mg, 244.57 μmol) in N,N-dimethylformamide (5 mL) was added N,N-diisopropylethylamine (94.83 mg, 733.72 μmol) and 1-methylpiperazine (48.99 mg, 489.15 μmol). The resulting mixture was stirred at 50 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **110-2**. MS m/z = 768.3 $[M+H]^+$.

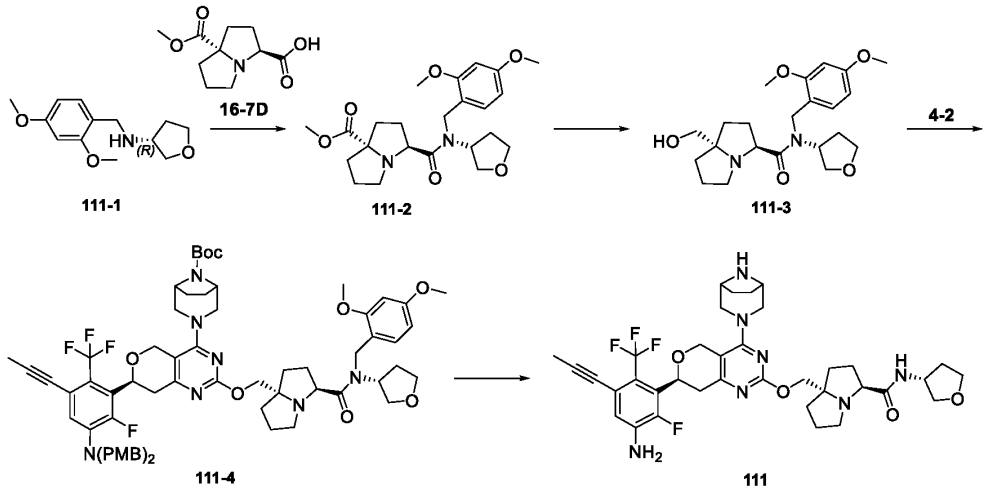
Step 3

To a stirred solution of compound **20-2D** (46.95 mg, 195.36 μmol) in dry THF (3 mL) was added sodium hydride (15.63 mg, 390.71 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **110-2** (100 mg, 130.24 μmol) was added, and the reaction was stirred at 25 °C for 1.5 hours. The reaction was quenched with saturated NH_4Cl solution (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **110-3.** MS m/z = 928.7 $[M+H]^+$.

Step 4

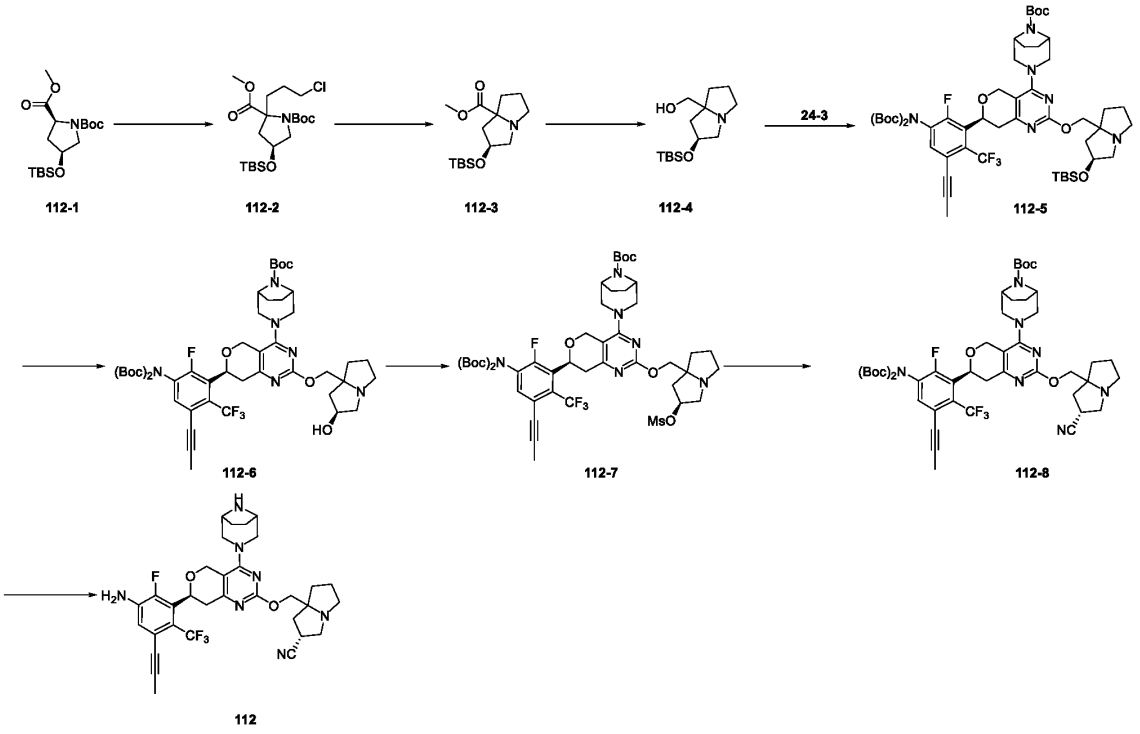
To a solution of compound **110-3** (100 mg, 107.75 μmol) in DCM (5 mL) was added TFA (2 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **110**. MS m/z = 688.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 8.0 Hz, 1H), 3.85 - 3.74 (m, 1H), 3.63 - 3.56 (m, 2H), 3.48 - 3.43 (m, 2H), 3.24 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.03 - 2.99 (m, 1H), 2.87 (dd, *J* = 20.0, 4.0 Hz, 2H), 2.67 - 2.58 (m, 2H), 2.57 - 2.49 (m, 2H), 2.35 (s, 3H), 2.21 - 2.13 (m, 2H), 2.02 (s, 3H), 1.97 - 1.88 (m, 5H), 1.80 - 1.75 (m, 1H), 1.36 (s, 9H).

Example 111



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **111-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-60%) to afford compound **111**. MS m/z = 714.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.41 - 4.36 (m, 1H), 4.18 - 4.13 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.92 (q, *J* = 8.0 Hz, 1H), 3.88 - 3.75 (m, 3H), 3.64 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.59 - 3.53 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.78 - 2.71 (m, 1H), 2.27 - 2.17 (m, 1H), 2.15 - 2.07 (m, 2H), 2.05 - 1.97 (m, 5H), 1.95 - 1.82 (m, 7H), 1.77 - 1.68 (m, 2H).

Example 112



Step 1

To a stirred solution of compound **112-1** (1 g, 2.78 mmol) in dry THF (10 mL) was added lithium bis(trimethylsilyl)amide (930.79 mg, 5.56 mmol,1 M in THF) at -78 °C and the mixture was stirred at -78 °C for 0.5 hours. Then 1-chloro-3-iodopropane (852.93 mg, 4.17 mmol) was added at -78 °C, and the reaction was stirred at 25 °C for 3 hours. The reaction was quenched with water, extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **112-2**. MS m/z = 436.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **112-2** (800 mg, 1.83 mmol) in DCM (10 mL) was addedzinc bromide (1.24 g, 5.50 mmol) and the mixture was stirred at 25 °C for 3 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was redissolved in acetonitrile (8 mL), K_2CO_3 (507.11 mg, 3.67 mmol) was added. The reaction was stirred at 25 °C for 3 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **112-3**. MS m/z =300.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **112-3** (1.00 g, 3.34 mmol) in dry THF (10 mL) was added lithium aluminum hydride (380.20 mg, 10.02 mmol，2.5 M in THF) at 0 °C. The reaction was stirred

at 0 °C for 1 hour. The reaction was diluted with DCM (50 mL), quenched with water (0.4 mL), 15% NaOH solution (0.4 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 10 minutes. The reaction was filtered, the filter was washed with DCM (10 mL), the filtrate was concentrated under reduced pressure to afford compound **112-4.** MS m/z = 272.0 $[M+H]^+$.

Step 4

To a stirred solution of compound **112-4** (145.45 mg, 535.78 μmol) in dry THF (2 mL) was added sodium hydride (12.86 mg, 535.78 μmol, 60% purity) and the mixture was stirred at 25 °C for 0.5 hours. Then compound **24-3** (300 mg, 357.19 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH = 15:1) to afford compound **112-5**. MS m/z = 1031.7 $[M+H]^+$.

Step 5

A solution of compound **112-5** (130.00 mg, 126.06 μmol) in tetrabutylammonium fluoride (0.5 mL, 1 M in THF) was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 15:1) to afford compound **112-6**. MS m/z = 817.6 $[M+H\text{-}Boc]^+$.

Step 7

To a stirred solution of compound **112-6** (80.00 mg, 87.24 μmol) in DCM (2 mL) was added triethyl amine (26.48 mg, 261.72 μmol) and methanesulfonyl chloride (22.49 mg, 196.29 μmol). The mixture was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih DCMc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **112-7**. MS m/z = 895.6 $[M+H\text{-}Boc]^+$. The crude product was used in the next step directly.

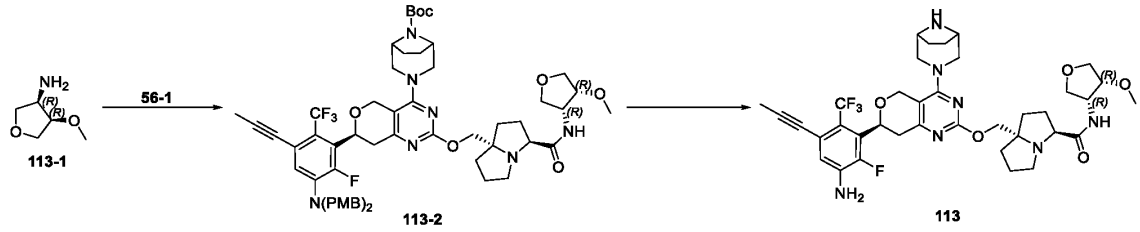
Step 8

To a stirred solution of compound **112-7** (120.00 mg, crude) in DCM (2 mL) was added triethyl amine (17.66 mg, 174.48 μmol) and sodium cyanide (14.99 mg, 130.86 μmol) and the mixture was stirred at 70 °C for 4 hours. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 15:1) to afford compound **112-8.** MS m/z =826.4 $[M+H\text{-}Boc]^+$.

Step 9

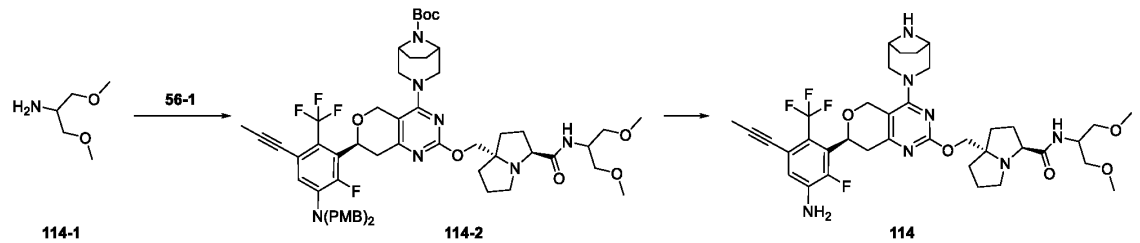
To a solution of compound **112-8** (20 mg, 21.60 μmol) in DCM (1 mL) was added TFA (0.5 mL), the mixture was stirred at 20 °C for 2 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 20%-70%) to afford compound **112**. MS m/z = 626.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.32 - 3.97 (m, 3H), 3.61 - 3.50 (m, 3H), 3.50 - 3.39 (m, 1H), 3.30 - 3.20 (m, 2H), 3.19 - 3.16 (m, 2H), 3.15 - 3.10 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.88 - 2.83 (m, 1H), 2.70 - 2.54 (m, 1H), 2.23 (d, *J* = 8.0 Hz, 2H), 2.15 - 2.03 (m, 2H), 2.01 (s, 3H), 1.91 - 1.76 (m, 4H), 1.77 - 1.62 (m, 2H).

Example 113



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **113-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **113**. MS m/z = 744.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.45 (dd, *J* = 16.0, 8.0 Hz, 1H), 4.22 - 4.11 (m, 2H), 4.07 (d, *J* = 8.0 Hz, 1H), 4.03 - 3.80 (m, 5H), 3.61 - 3.47 (m, 4H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.37 (s, 3H), 3.22 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.09 - 2.96 (m, 2H), 2.90 - 2.69 (m, 2H), 2.17 - 2.07 (m, 2H), 2.06 - 1.77 (m, 11H), 1.77 - 1.64 (m, 2H).

Example 114



Step 1

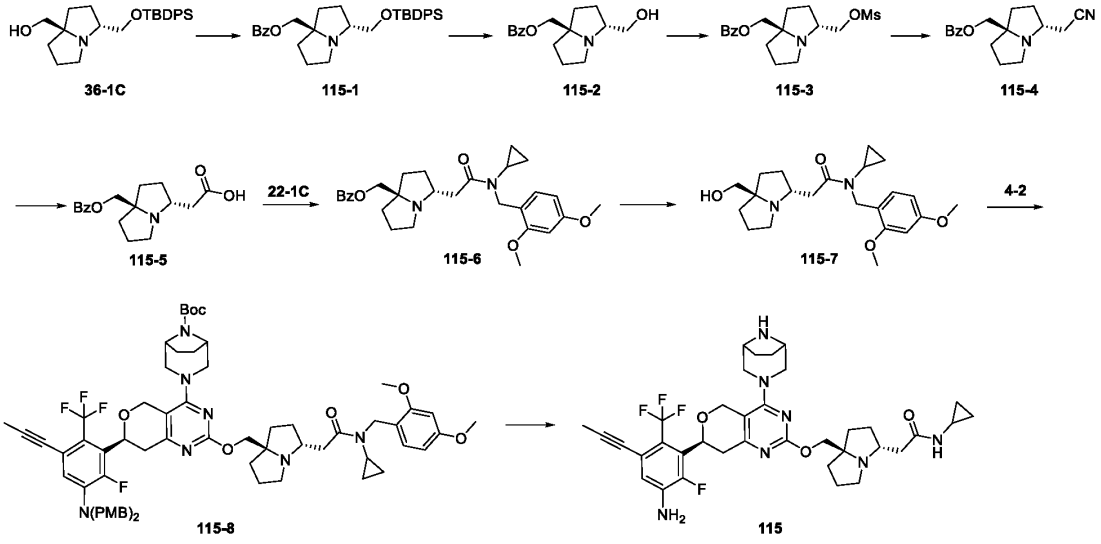
To a stirred solution of compound **56-1** (35 mg, 35.53 μmol) in DCM (2 mL) was added N,N-

diisopropylethylamine (22.96 mg, 177.65 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (22.97 mg, 60.40 μmol) and compound **114-1** (8.47 mg, 71.06 μmol). The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **114-2**. MS m/z = 1086.8 $[M+H]^+$.

Step 2

To a solution of compound **114-2** (17 mg, 15.65 μmol) in DCM (0.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **114**. MS m/z = 746.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.21 - 4.11 (m, 3H), 4.06 (d, J = 12.0 Hz, 1H), 3.80 - 3.76 (m, 1H), 3.56 - 3.51 (m, 3H), 3.48 - 3.41 (m, 5H), 3.34 (d, J = 4.0 Hz, 6H), 3.25 - 3.18 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.98 - 2.93 (m, 1H), 2.85 (dd, J = 12.0, 4.0 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.14 - 2.07 (m, 2H), 2.04 - 1.98 (m, 5H), 1.95 - 1.89 (m, 4H), 1.86 - 1.81 (m, 2H), 1.77 - 1.68 (m, 2H).

Example 115



Step 1

To a stirred solution of compound **36-1C** (800 mg, 1.95 mmol) in dry DCM (10 mL) was added triethyl amine (592.86 mg, 5.86 mmol) and benzoyl chloride (549.04 mg, 3.91 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched with water (10 mL), extracted

wtih DCM (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **115-1**. MS m/z = 514.4 $[M+H]^+$.

Step 2

The mixture of compound **115-1** (900 mg, 1.75 mmol) and HCl (15 mL, 4 M in dioxane) was stirred at 50 °C for 48 hours. The reaction was concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL), washed wtih saturated $NaHCO_3$ solution (15 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **115-2**. MS m/z = 276.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **115-2** (420 mg, 1.53 mmol) in DCM (10 mL) was added triethyl amine (617.41 mg, 6.10 mmol) and methanesulfonyl chloride (349.47 mg, 3.05 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched with water (10 mL), extracted wtih DCM (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **115-3**. MS m/z = 354.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **115-3** (460 mg, 1.30 mmol) in N,N-dimethylformamide (10 mL) was added sodium cyanide (138.06 mg, 2.60 mmol) and the mixture was stirred at 80 °C for 16 hours. Then saturated $NaHCO_3$ solution was added to adjust pH = 9, extracted wtih EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **115-4**. MS m/z = 285.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **115-4** (300 mg, 1.06 mmol) in dioxane (10 mL) was added concentrated HCl (3 mL, 1.06 mmol, 12 M) and the mixture was stirred at 50 °C for 20 hours. Then saturated $NaHCO_3$ solution was added to adjust pH = 6. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 [ACN-H_2O (0.1% NH_4HCO_3); Gradient: (ACN): 0%-5%] to afford compound **115-5**. MS m/z = 304.2 $[M+H]^+$.

Step 6

To a stirred solution of compound **115-5** (280 mg, 923.02 μmol) in N,N-dimethylformamide (5 mL) was added N,N-diisopropylethylamine (357.88 mg, 2.77 mmol) and O-(7-Azabenzotriazol-1-

yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (526.44 mg, 1.38 mmol). The mixture was stirred at 25 °C for 3 hours. The reaction was quenched with water (10 mL), extracted wtih DCM (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **115-6**. MS m/z = 493.4 $[M+H]^+$.

Step 7

To a stirred solution of compound **115-6** (70 mg, 142.10 μmol) in MeOH (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (17.89 mg, 426.30 μmol) and the mixture was stirred at 25 °C for 1 hour. The reaction was filtered, the filter was washed with MeOH (5 mL), the filtrate was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 [ACN-H_2O (0.1% NH_4HCO_3); Gradient: (ACN): 0%-35%] to afford compound **115-7**. MS m/z = 389.4 $[M+H]^+$.

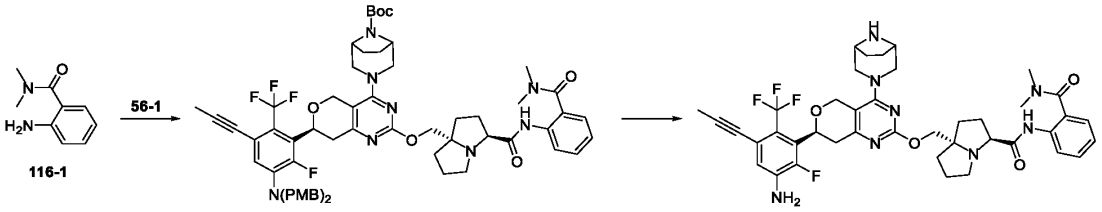
Step 8

To a stirred solution of compound **115-7** (45 mg, 115.83 μmol) in dry THF (2 mL) was added sodium hydride (6.95 mg, 173.75 μmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (225 mg, 255.69 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **115-8**. MS m/z = 1188.9 $[M+H]^+$.

Step 9

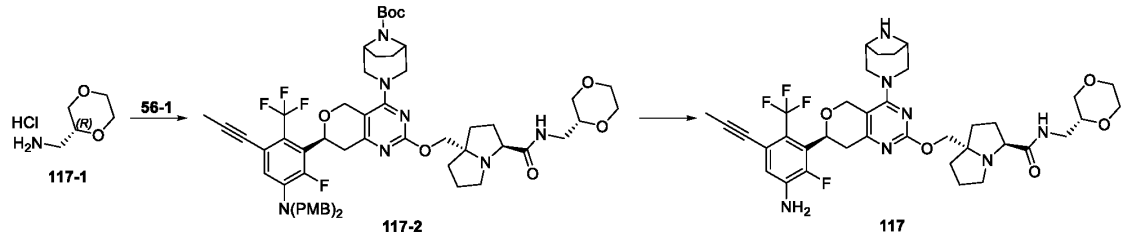
To a solution of compound **115-8** (70 mg, 58.91 μmol) in DCM (2 mL) was added TFA (0.6 mL), the mixture was stirred at 35 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: sunfire-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 32%-52%) to afford compound **115**. MS m/z = 698.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (s, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.40 (q, *J* = 12.0 Hz, 2H), 4.15 (d, *J* = 12.0 Hz, 1H), 3.91 (s, 1H), 3.71 (s, 2H), 3.62 (d, *J* = 12.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.28 - 3.23 (m, 1H), 3.14 (d, *J* = 12.0 Hz, 1H), 3.10 - 3.01 (m, 1H), 2.95 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.69 - 2.55 (m, 3H), 2.36 - 2.31 (m, 1H), 2.15 - 2.02 (m, 8H), 1.98 - 1.86 (m, 6H), 1.82 - 1.75 (m, 1H), 0.73 - 0.64 (m, 2H), 0.50 - 0.42 (m, 2H).

Example 116



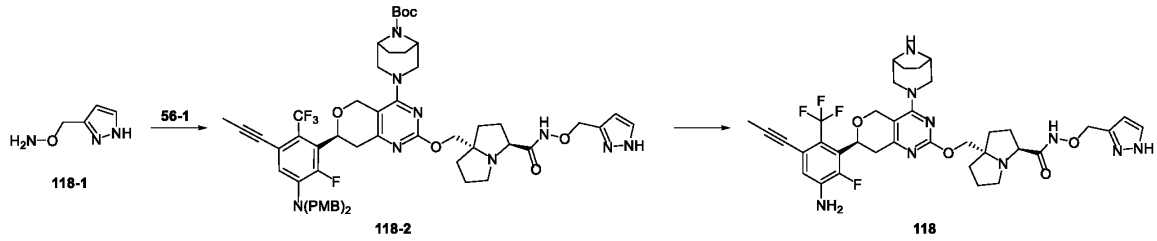
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **116-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-90%) to afford compound **116**. MS m/z = 791.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.58 (d, *J* = 8.0 Hz, 1H), 7.45 (td, *J* = 8.0, 4.0 Hz, 1H), 7.34 - 7.26 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 8.0 Hz, 1H), 3.97 - 3.94 (m, 1H), 3.62 - 3.55 (m, 3H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.23 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.09 - 3.03 (m, 5H), 2.98 (s, 3H), 2.89 - 2.77 (m, 2H), 2.19 - 2.10 (m, 3H), 2.05 - 2.02 (m, 4H), 1.99 - 194 (m, 3H), 1.90 - 1.84 (m, 2H), 1.81 - 1.71 (m, 3H).

Example 117



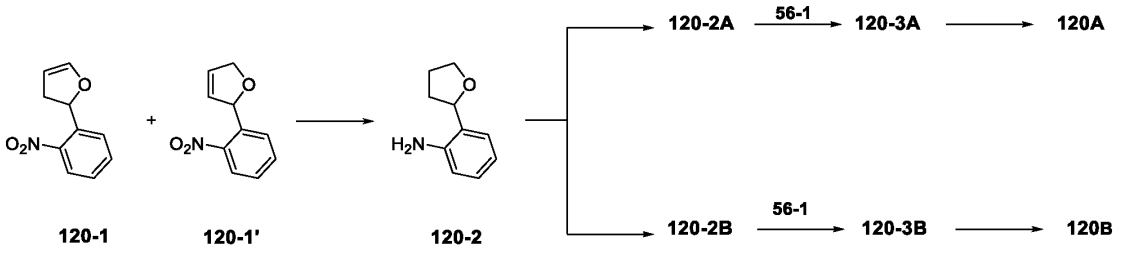
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **117-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **117**. MS m/z = 744.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.79 - 3.73 (m, 3H), 3.70 - 3.61 (m, 3H), 3.59 - 3.52 (m, 4H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.36 - 3.33 (m, 1H), 3.27 (d, *J* = 12.0 Hz, 1H), 3.23 - 3.14 (m, 2H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.96 - 2.90 (m, 1H), 2.85 (dd, *J* = 20.0, 8.0 Hz, 1H), 2.78 - 2.69 (m, 1H), 2.14 - 2.06 (m, 2H), 2.05 - 1.97 (m, 5H), 1.95 - 1.81 (m, 6H), 1.76 - 1.67 (m, 2H).

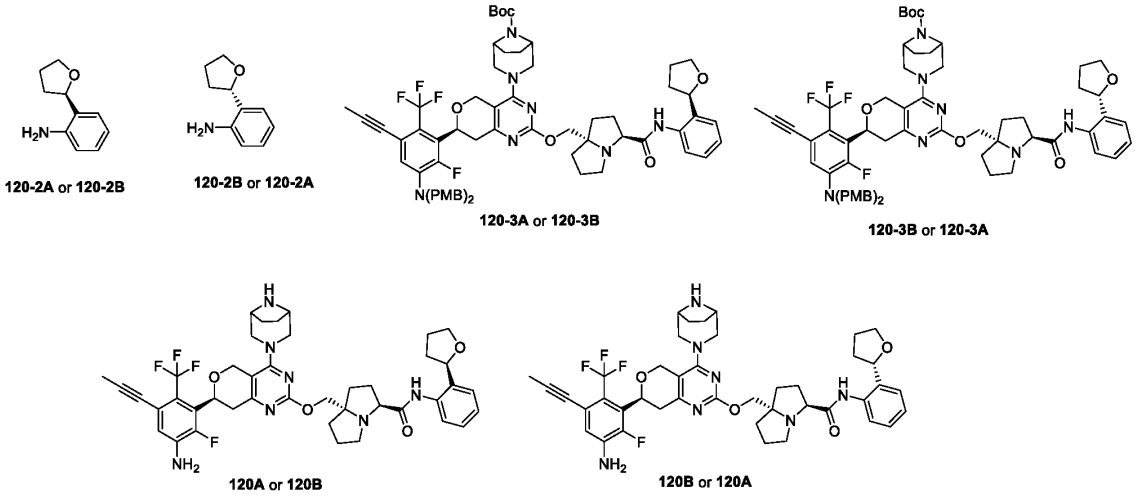
Example 118



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **118-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-68%) to afford compound **118**. MS m/z = 740.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.60 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.44 (s, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.91 (s, 2H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.16 - 4.12 (m, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.61 (t, *J* = 4.0 Hz, 1H), 3.56 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.76 (m, 3H), 2.12 - 2.05 (m, 3H), 2.04 - 1.96 (m, 7H), 1.89 - 1.79 (m, 3H), 1.77 - 1.67 (m, 2H).

Example 120





Step 1

To a stirred solution of compound **120-1** and **120-1'** (4.4 g, 23.01 mmol) in MeOH (100 mL) was added Pd/C (1.1 g, 10.36 mmol, 10% purity) and triethyl amine (11.64 g, 115.07 mmol). The mixture was stirred at 25 °C for 16 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, was washed with MeOH (10 mL), the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **120-2**. MS m/z = 164.1 $[M+H]^+$. The compound **120-2** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®IC-10, 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH(0.05% DEA); Gradient: B% 10%) to afford compound **122-2A** and compound **122-2B**. SFC Analysis methods (chromatographic column: DAICEL CHIRALPAK®IC-3 (100*3 mm 3 μm); Mobile phase: A: Supercritical CO_2; B: MeOH(0.05% DEA); Gradient: B% 5%-40%, 4 min). Compound **122-2A**, Rt = 2.158 mins, ee: 100%, MS m/z = 164.1 $[M+H]^+$; compound **122-2B**, Rt = 2.39 mins, ee: 100%, MS m/z = 164.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **56-1** (20 mg, 20.30 μmol) in DCM (1 mL) was added N,N-diisopropylethylamine (7.87 mg, 60.91 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (13.12 mg, 34.52 μmol) and compound **120-2A** (4.97 mg, 30.45 μmol). The resulting mixture was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **120-3A**. MS m/z = 1130.8 $[M+H]^+$.

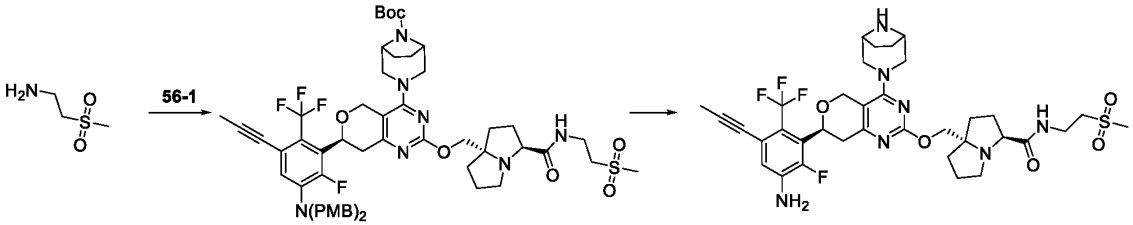
With reference to step 2, compound **120-2A** was replaced with compound **120-2B** as the raw material to obtain compound **120-3B**. MS m/z = 1130.8 $[M+H]^+$.

Step 3

To a solution of compound **120-3A** (15 mg, 13.27 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **120A**. MS m/z = 790.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.69 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 4.0, 1H), 7.30 - 7.26 (m, 1H), 7.22 - 7.14 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.98 - 4.95 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.27 - 4.08 (m, 4H), 4.02 - 3.98 (m, 1H), 3.89 - 3.84 (m, 1H), 3.56 - 3.47 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.13 - 3.01 (m, 2H), 2.91 - 2.74 (m, 2H), 2.37 - 2.27 (m, 1H), 2.21 - 1.91 (m, 13H), 1.86 - 1.65 (m, 5H).

To a solution of compound **120-3B** (20 mg, 17.69 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **120B**. MS m/z = 790.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.68 (dd, J = 8.0, 4.0 Hz, 1H), 7.39 - 7.37 (m, 1H), 7.30 - 7.26 (m, 1H), 7.21 - 7.17 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 5.01 - 4.95 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.24 (d, J = 8.0 Hz, 1H), 4.19 - 4.07 (m, 3H), 3.98 (dd, J = 8.0, 4.0 Hz, 1H), 3.89 - 3.83 (m, 1H), 3.61 - 3.48 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.09 - 2.95 (m, 2H), 3.88 - 2.78 (m, 2H), 2.39 - 2.29 (m, 1H), 2.24 - 1.89 (m, 13H), 1.86 - 1.64 (m, 5H).

Example 121

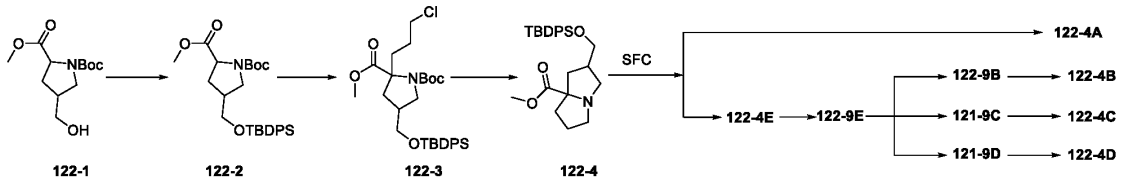


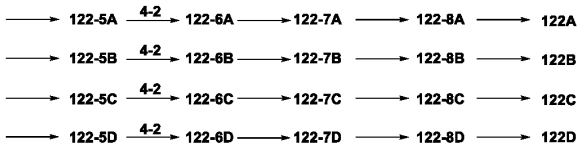
121-1 121-2 121

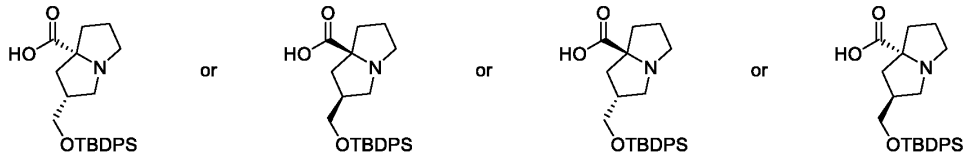
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **121-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **121**. MS m/z = 750.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.79 - 3.75 (m, 1H), 3.71 - 3.67 (m, 2H), 3.59 - 3.53 (m, 3H), 3.45-3.42 (m, 1H), 3.36 - 3.34 (m, 2H), 3.25-3.18 (m, 1H),

3.06 (d, J = 12.0 Hz, 1H), 3.01 (s, 3H), 2.98 - 2.95 (m, 1H), 2.87 - 2.82 (m, 1H), 2.76 - 2.70 (m, 1H), 2.14 - 2.09 (m, 2H), 2.04 - 1.99 (m, 5H), 1.96 - 1.85 (m, 6H), 1.77-1.69 (m, 2H).

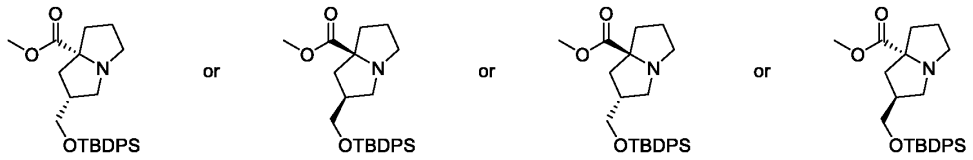
Example 122



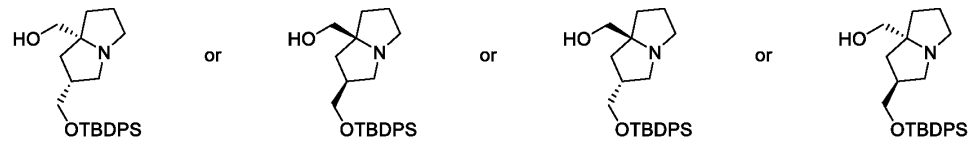




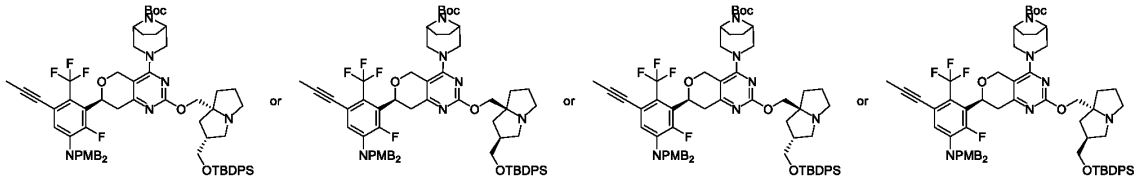
122-9B (single isomer) or **122-9C** (single isomer) or **122-9D** (single isomer)
122-9E(mixture of 3 isomers)



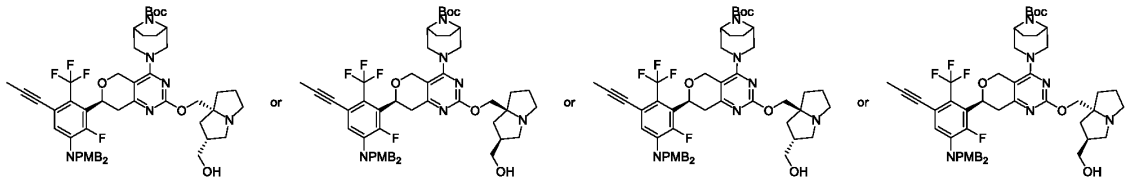
122-4A (single isomer) or **122-4B** (single isomer) or **122-4C** (single isomer) or **122-4D** (single isomer)
122-4E(mixture of 3 isomers)



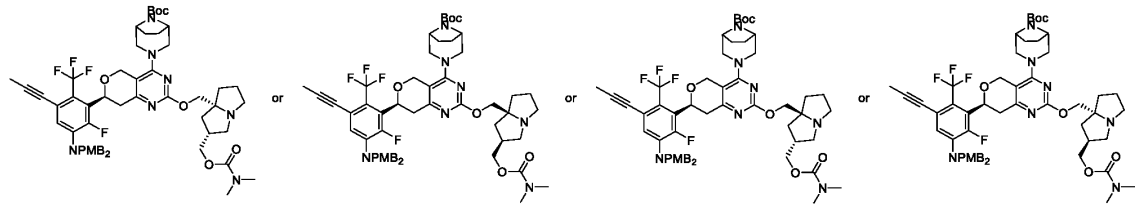
122-5A or **122-5B** or **122-5C** or **122-5D**



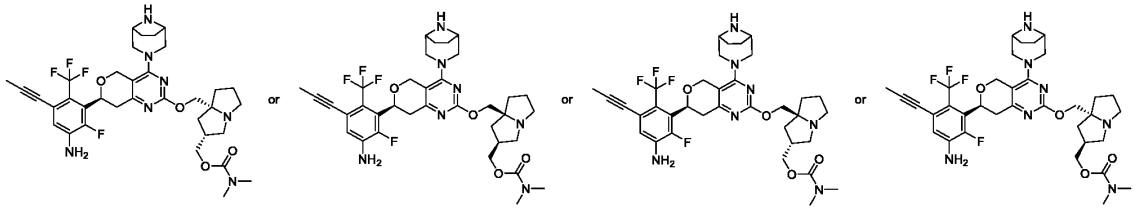
122-6A or 122-6B or 122-6C or 122-6D



122-7A or 122-7B or 122-7C or 122-7D



122-8A or 122-8B or 122-8C or 122-8D



122A or 122B or 122C or 122D

Step 1

To a stirred solution of compound **122-1** (4.4g,16.97 mol) in DCM (40 mL) was added imidazole (2.31g, 33.94mmol) and tert-butylchlorodiphenylsilane (7g, 25.45 mmol). The reaction was stirred at 25 °C for 16 hours. The reaction was quenched with water (50 mL), extracted wtih DCM (3 × 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **122-2**. MS m/z = 498.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **122-2** (5.6 g, 11.25 mmol) in dry THF (60 mL) was added lithium bis(trimethylsilyl)amide (1 M, 16.88 mmol, 16.88 mL,) at -78 °C and the mixture was stirred at -78 °C for 0.5 hours. Then 1-chloro-3-iodopropane (3.45 g, 16.88 mmol) was added at -78 °C, and the reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (50 mL), extracted wtih EtOAc (3 × 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **122-3**. MS m/z = 574.1 $[M+H]^+$.

Step 3

To a stirred solution of compound **122-3** (5.7 g, 9.93mmol) in DCM (100 mL) was added zinc bromide (6.71g, 29.78 mmol) and the mixture was stirred at 25 °C for 16 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **122-4**. MS m/z = 438.4 $[M+H]^+$. The compound **122-4** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®OJ-10, 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: (0.05% EtOH - DEA); Gradient: B% 10%) to afford compound **122-4A** and compound **122-4E** (mixture of isomers). SFC Analysis methods (chromatographic column: ChiralPak OJ-3(100mm*4.6mm,3μm); Mobile phase: A: Supercritical CO_2; B: (0.05% EtOH - DEA); Gradient: B% 5%-40%). Compound **122-4A**, Rt = 2.621 mins, MS m/z = 438.4 $[M+H]^+$; compound **122-4E**, Rt = 1.912-2.026 mins, MS m/z = 438.4 $[M+H]^+$.

Step 4

To a stirred solution of compound **122-4E** (2.0 g, 4.57 mmol) in THF (20 mL) and water (5 mL) was added lithium hydroxide (547.21 mg, 20.85 mmol). The resulting mixture was stirred at 25 °C for 16 hours. The reaction was quenched with saturated NH_4Cl solution (20 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **122-9E** (mixture of isomers). MS m/z = 424.2 $[M+H]^+$. The compound **122-9E** was separated by preparative SFC (Column name: DAICEL CHIRALPAK®IC-10, 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: (0.05% NH_3/MeOH - EtOH); Gradient: B% 40%) to afford compound **122-9B**, **122-9C** and **122-9D**. SFC Analysis methods (chromatographic column: ChiralPak IC-3(100mm*4.6mm,3μm); Mobile phase: A: Supercritical CO_2; B: (EtOH - 0.05% NH_3/MeOH); Gradient: B% 5%-40%). Compound **122-9B**, Rt = 6.561 mins, MS m/z = 424.2 $[M+H]^+$; compound **122-9C**, Rt = 7.912 mins, MS m/z = 424.2 $[M+H]^+$; compound **122-9D**, Rt = 10.380 mins, MS m/z = 424.2 $[M+H]^+$.

Step 5

To a stirred solution of compound **122-9B** (450 mg, 1.06 mmol) in DCM (6 mL) was added oxalyl chloride (269.66 mg, 2.12 mmol) slowly at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. The above reactiom mixture was added to MeOH (6 mL) slowly at 0 °C and the resulting mixture was stirred at 0 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **122-4B**.MS m/z = 438.3 $[M+H]^+$.

With reference to step 5, compound **122-9B** was replaced with compound **122-9C** as the raw

material to obtain compound **122-4C**. MS m/z = 438.3 $[M+H]^+$.

With reference to step 5, compound **122-9B** was replaced with compound **122-9D** as the raw material to obtain compound **122-4D**. MS m/z = 438.3 $[M+H]^+$.

Step 6

With reference to steps 11~15 of **Example 36**, compound **16-5C** was replaced with compound **122-4A** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-70%) to afford compound **122A** as FA salt. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (s, 1.77H), 6.88 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 5.05 - 5.01 (m, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.02 - 3.86 (m, 5H), 3.69 (s, 2H), 3.45 (d, J = 12.0 Hz, 1H), 3.36 (d, J = 12.0 Hz, 1H), 3.16 - 2.99 (m, 3H), 2.81 - 2.72 (m, 8H), 2.67 - 2.60 (m, 3H), 2.32 - 2.27 (m, 1H), 2.09 - 1.65 (m, 12H), 1.33 - 1.30 (m, 1H).

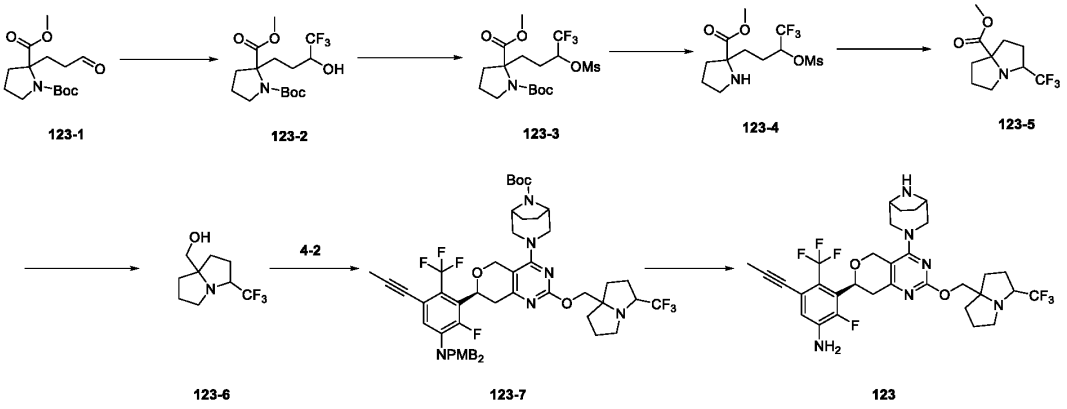
With reference to steps 11~15 of **Example 36**, compound **16-5C** was replaced with compound **122-4B** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-70%) to afford compound **122B** as FA salt. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO - d_6) δ ppm 8.24 (s, 1.63H), 6.88 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 5.06 - 5.01 (m, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.04 - 3.87 (m, 5H), 3.68 - 3.65 (m, 2H), 3.44 (d, J = 12.0 Hz, 1H), 3.35 (d, J = 12.0 Hz, 1H), 3.10 - 2.97 (m, 3H), 2.87 - 2.74 (m, 8H), 2.68 - 2.52 (m, 3H), 2.49 - 2.40 (m, 1H), 2.03 (s, 3H), 1.98 - 1.83 (m, 3H), 1.82 - 1.62 (m, 5H), 1.60 - 1.49 (m, 2H).

With reference to steps 11~15 of **Example 36**, compound **16-5C** was replaced with compound **122-4C** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-70%) to afford compound **122C** as FA salt. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO - d_6) δ ppm 8.25 (s, 1.95H), 6.88 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 5.06 - 5.00 (m, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.02 - 3.89 (m, 5H), 3.64 - 3.58 (m, 2H), 3.42 (d, J = 12.0 Hz, 1H), 3.33 (d, J = 12.0 Hz, 1H), 3.10 - 2.94 (m, 3H), 2.85 - 2.72 (m, 8H), 2.68 - 2.51 (m, 3H), 2.47 - 2.38 (m, 1H), 2.03 (s, 3H), 1.97 - 1.62 (m, 8H), 1.57 - 1.49 (m, 2H).

With reference to steps 11~15 of **Example 36**, compound **16-5C** was replaced with compound **122-4D** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-70%) to afford compound **122D** as FA salt. MS m/z = 702.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.24 (s, 1.30H), 6.88 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 5.11 - 4.99 (m, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.04 - 3.83 (m, 5H), 3.67 (s, 2H), 3.53 - 3.28 (m,

2H), 3.17 - 2.81 (m, 11H), 2.68 - 2.51 (m, 2H), 2.32 - 2.27 (m, 1H), 2.11 - 2.05 (m, 1H), 2.03 (s, 3H), 1.97 - 1.54 (m, 9H), 1.31 (t, J = 9.0 Hz, 1H).

Example 123



Step 1

To a stirred solution of compound **123-1** (800 mg, 2.81 mmol) in dry THF (10 mL) was added (trifluoromethyl)trimethylsilane (598 mg, 4.21 mmol) and tetrabutylammonium fluoride (2.8 mL, 1 M in THF) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **123-2**. MS m/z = 356.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **123-2** (350 mg, 0.98 mmol) in DCM (5 mL) was added triethyl amine (200 mg, 1.97 mmol) and methanesulfonyl chloride (226 mg, 1.97 mmol). The mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford crude compound **123-3**. MS m/z = 434.1 $[M+H]^+$.

Step 3

A solution of compound **123-3** (350 mg, crude) in HCl (5 mL, 4 M in dioxane) was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure to afford crude compound **123-4**. MS m/z = 334.1 $[M+H]^+$.

Step 4

To a stirred solution of compound **123-4** (250 mg, crude) in acetonitrile (8 mL) was added K_2CO_3 (311 mg, 2.25 mmol). The reaction was stirred at 65 °C for 16 hours. The reaction was filtered, the

filtrate was concentrated under reduced pressure to afford crude compound **123-5**. MS m/z = 238.1 $[M+H]^+$.

Step 5

To a stirred solution of compound **123-5** (100 mg, crude) in dry THF (2 mL) was added lithium aluminum hydride (0.8 mL, 0.83 mmol, 1 M) at 0 °C. The reaction was stirred at 25 °C for 1 hour. The reaction was quenched with sodium sulfate decahydrate, filtered, the filtrate was concentrated under reduced pressure to afford crude compound **123-6**. MS m/z = 210.2 $[M+H]^+$.

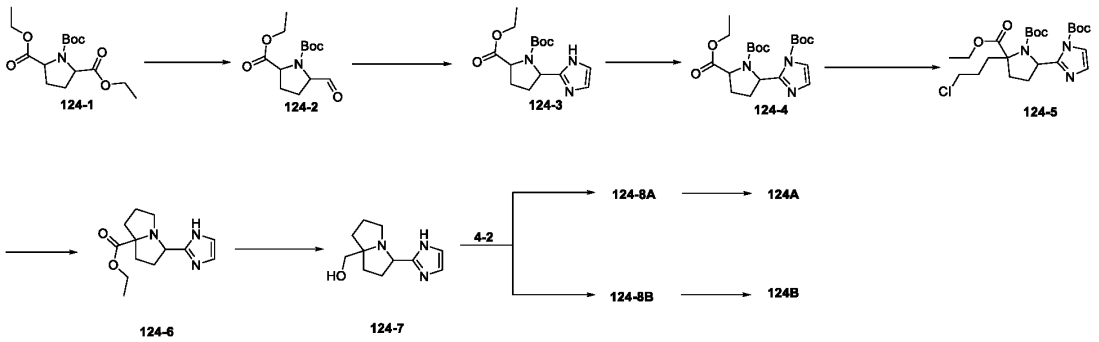
Step 6

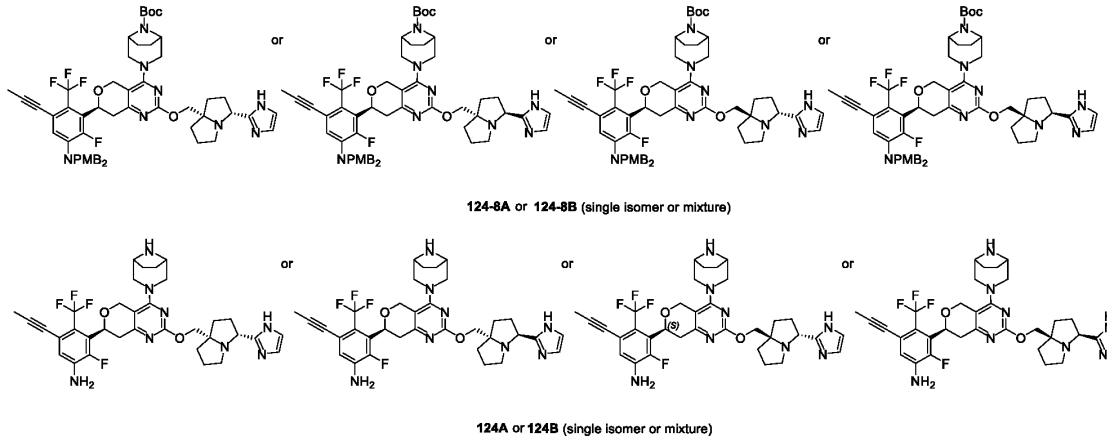
To a stirred solution of compound **123-6** (70 mg, crude) in dry THF (2 mL) was added sodium hydride (31.33 mg, 0.78 mmol, 60% purity) at 0 °C and the mixture was stirred at 0 °C for 0.5 hours. Then compound **4-2** (294 mg, 0.33 mmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (2 mL), extracted wtih EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:2) to afford compound **123-7**. MS m/z = 1009.6 $[M+H]^+$.

Step 7

The mixture of compound **123-7** (40 mg, 39.64 μmol) in TFA (1 mL) was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge C18 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 55%-80%) to afford compound **123**. MS m/z = 669.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.81 - 4.77 (m, 2H), 4.67 (d, J = 16.0 Hz, 1H), 4.19 - 4.15 (m, 2H), 4.10 - 4.17 (m, 1H), 3.83 - 3.82 (m, 2H), 3.63 - 3.59 (m, 1H), 3.53 - 3.48 (m, 1H), 3.24 - 3.13 (m, 3H), 2.96 - 2.84 (m, 2H), 2.10 - 2.09 (m, 3H), 2.05 - 2.01 (m, 7H), 1.9 - 1.89 (m, 4H), 1.62 - 1.59 (m, 1H).

Example 124





124-8A or 124-8B (single isomer or mixture)

124A or 124B (single isomer or mixture)

Step 1

To a stirred solution of compound **124-1** (1.55 g, 4.92 mol) in dry diethyl ether (20 mL) was added diisobutylaluminium hydride (7.38 mol, 7.38 mL, 1 M in THF) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with water (0.1 mL) and saturated NH_4Cl solution (15 mL) at 0 °C, extracted wtih EtOAc (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **124-2**. MS m/z = 272.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **124-2** (600 mg, 2.21 mmol) in MeOH (15 mL) was added glyoxal (1.28 mL, 8.85 mmol, 40% in water) and ammonium hydroxide (1.86 mL, 13.27 mmol, 25% in water). The reaction was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was diluted with water (10 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **124-3**. MS m/z = 310.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **124-3** (200 mg, 646.50 μmol) in DCM (5 mL) was added di-tert-butyl dicarbonate (282 mg,1.29 mmol), triethyl amine (196 mg, 1.94 mmol) and 4-dimethylaminopyridine (15.8 mg, 129.3 μmol). The reaction was stirred at 25 °C for 2 hours. The reaction was diluted with water (15 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **124-4**. MS m/z = 410.3 $[M+H]^+$.

Step 4

To a stirred solution of compound **124-4** (210 mg, 512.80 μmol) in dry THF (10 mL) was added LiHMDS (1.03 mmol, 1.03 mL, 1 M in THF) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 30 minutes. Then 1-chloro-3-iodopropane (209 mg,1.03 mmol) was added and

the resulting mixture was stirred at 25 °C for 2 hours. The reaction was diluted with water (15 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **124-5**. MS m/z = 486.3 $[M+H]^+$.

Step 5

To a stirred solution of compound **124-5** (140 mg, 288.07 μmol) in DCM (5 mL) was added HCl (0.5 mL, 4 M in EtOAc) and the mixture was stirred at 25 °C for 30 minutes. The reaction was concentrated under reduced pressure. The residue was redissolved in MeOH (5 mL), ammonia (0.2 mL, 1.4 mmol, 7 M in MeOH) was added and the resulting mixture was stirred at 25 °C for 30 minutes. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **124-6**. MS m/z = 250.0 $[M+H]^+$.

Step 6

To a stirred solution of compound **124-6** (90 mg, 361 μmol) in dry THF (10 mL) was added lithium aluminum hydride (541.5 μL, 541.5 μmol, 1 M in THF) at 0 °C under nitrogen atmosphere. The reaction was stirred at 0 °C for 2 hours. The reaction was diluted with DCM (50 mL), quenched wtih water (0.2 mL), 15% NaOH solution (0.2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes, filtered, the filter was washed with DCM (10 mL). The filtrate was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **124-7**. MS m/z = 208.2 $[M+H]^+$.

Step 7

To a stirred solution of compound **124-7** (40 mg, 192.98 μmol) in dry THF (5 mL) was added sodium hydride (23.16 mg, 964.92 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **4-2** (169.82 mg, 192.98 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **124-8A** (DCM: MeOH = 10:1, Rf = 0.45), MS m/z = 1007.8 $[M+H]^+$ and compound **124-8B** (DCM: MeOH = 10:1, Rf = 0.4), MS m/z = 1007.8 $[M+H]^+$.

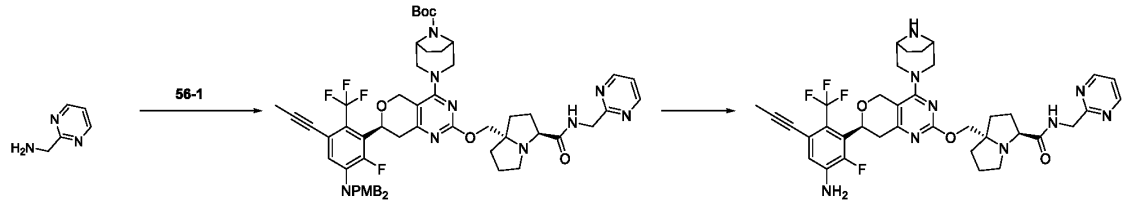
Step 8

To a solution of compound **124-8A** (28 mg, 27.80 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **124A**. MS m/z = 667.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.99 - 6.72 (m, 3H), 5.15 (dd, *J* = 12.0,

4.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.59 - 4.53 (m, 1H), 4.21 - 4.09 (m, 2H), 3.96 - 3.93 (m, 1H), 3.60 - 3.52 (m, 2H), 3.46 - 3.41 (m, 1H), 3.23 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.09 - 2.83 (m, 3H), 2.23 - 2.15 (m, 3H), 2.11 - 1.94 (m, 6H), 1.90 - 1.61 (m, 8H).

To a solution of compound **124-8 B** (56 mg, 55.60 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **124B**. MS m/z = 667.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.02 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.82 - 4.78 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.38 - 4.34 (m, 1H), 4.24 - 4.13 (m, 3H), 3.53 - 3.50 (m, 3H), 3.43 - 3.39 (m, 1H), 3.22 (dd, *J* = 20.0, 8.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.61 - 2.54 (m, 1H), 2.45 - 2.40 (m, 2H), 2.19 - 2.14 (m, 1H), 2.09 - 1.96 (m, 7H), 1.83 - 1.67 (m, 6H).

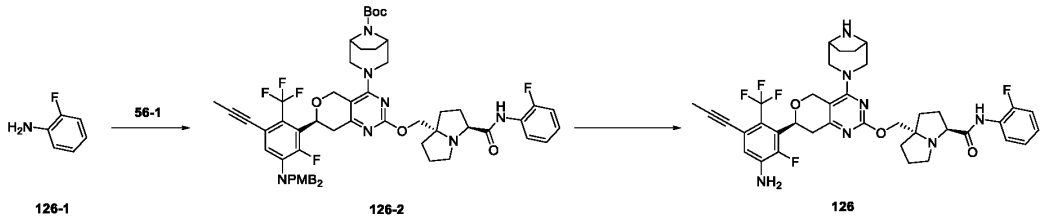
Example 125



125-1 125-2 125

With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **125-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 30%-70%) to afford compound **125** as FA salt. MS m/z = 736.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.74 (d, *J* = 4.0 Hz, 2H), 8.45 (brs, 0.91H),7.37 (t, *J* = 4.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.22 - 5.14 (m, 1H), 4.88 - 4.86 (m, 1H), 4.74 - 4.61 (m, 3H), 4.48 - 4.24 (m, 4H), 4.10 - 4.04 (m, 2H), 3.77 (d, *J* = 16.0 Hz, 1H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.54 - 3.45 (m, 1H), 3.31 - 3.24 (m, 2H), 3.23 - 3.10 (m, 1H), 2.92 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.51 - 2.31 (m, 2H) , 2.28 - 2.20 (m, 3H) , 2.12 - 2.07 (m, 4H) , 2.02 - 1.92 (m, 6H).

Example 126



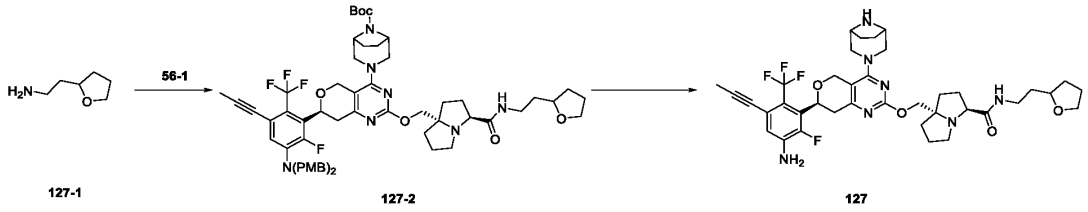
Step 1

To a stirred solution of compound **56-1** (50 mg, 50.76 μmol) in acetonitrile (1 mL) was added N-methylimidazole (8.75 mg, 106.59 μmol), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (15.67 mg, 55.83 μmol) and compound **126-1** (8.46 mg, 76.14 μmol). The mixture was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **126-2**. MS m/z = 1078.6 $[M+H]^+$.

Step 2

To a solution of compound **126-2** (17 mg, 15.77 μmol) in DCM (0.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **126**. MS m/z = 738.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.94 - 7.84 (m, 1H), 7.22 - 7.11 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 - 4.79 (m, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.26 - 4.16 (m, 2H), 4.12 (d, J = 12.0 Hz, 1H), 4.06 - 4.02 (m, 1H), 3.73 - 3.68 (m, 2H), 3.63 - 3.58 (m, 1H), 3.48 (d, J = 12.0 Hz, 1H), 3.28 - 3.19 (m, 1H), 3.14 - 3.08 (m, 1H), 3.06 - 3.01 (m, 1H), 2.91 - 2.81 (m, 2H), 2.25 - 2.06 (m, 5H), 2.04 - 1.99 (m, 4H), 1.97 - 1.90 (m, 4H), 1.81 - 1.75 (m, 2H).

Example 127



Step 1

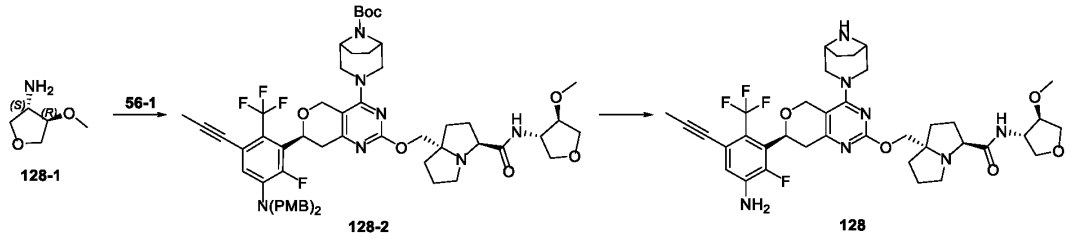
To a stirred solution of compound **56-1** (60 mg, 60.91 μmol) in acetonitrile (1 mL) was added N-methylimidazole (10.50 mg, 127.91 μmol), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (18.80 mg, 67.00 μmol) and compound **127-1** (10.52 mg, 91.36 μmol). The

mixture was stirred at 25 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **127-2**. MS m/z = 1082.7 $[M+H]^+$.

Step 2

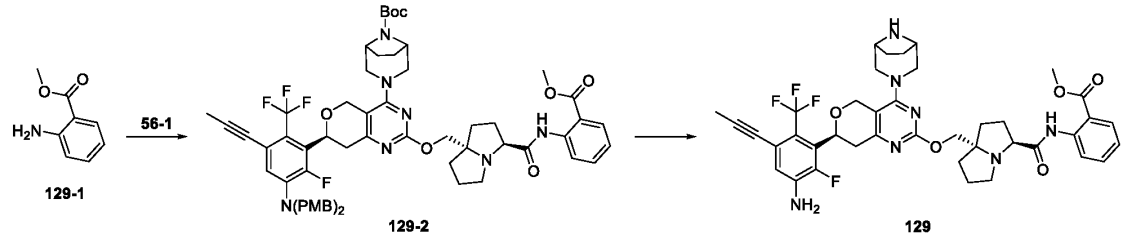
To a solution of compound **127-2** (15 mg, 13.86 μmol) in DCM (0.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **127**. MS m/z = 742.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.16 - 5.12 (m, 1H), 4.81- 4.77 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.89 - 3.82 (m, 2H), 3.77 - 3.65 (m, 2H), 3.56 - 3.46 (m, 3H), 3.45 - 3.36 (m, 1H), 3.35 - 3.32 (m, 1H), 3.29 - 3.15 (m, 2H), 3.04 (d, J = 12.0 Hz, 1H), 2.95 - 2.79 (m, 2H), 2.77 - 2.66 (m, 1H), 2.20 - 2.03 (m, 3H), 2.03 - 1.99 (m, 4H), 1.99 - 1.77 (m, 9H), 1.77 - 1.63 (m, 4H), 1.56 - 1.47 (m, 1H).

Example 128



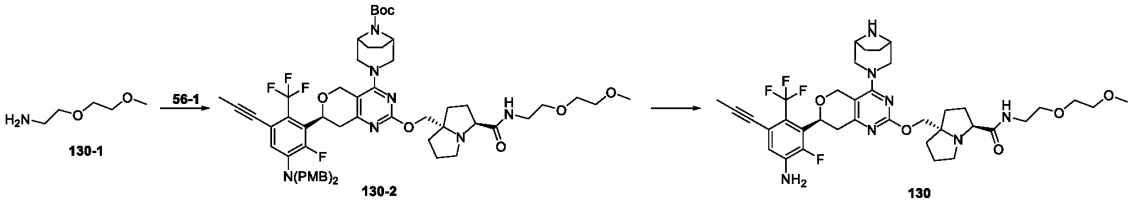
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **128-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 20%-42%) to afford compound **128**. MS m/z = 744.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.29 (s, 1H), 4.15 (t, J = 12.0 Hz, 2H), 4.05 (d, J = 12.0 Hz, 1H), 4.00 - 3.95 (m, 2H), 3.86 - 3.81 (m, 1H), 3.79 - 3.65 (m, 3H), 3.54 - 3.51 (m, 3H), 3.43 - 3.38 (m, 4H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.77 - 2.70 (m, 1H), 2.15 - 2.07 (m, 2H), 2.04 - 1.97 (m, 5H), 1.95 - 1.80 (m, 6H), 1.77 - 1.66 (m, 2H).

Example 129



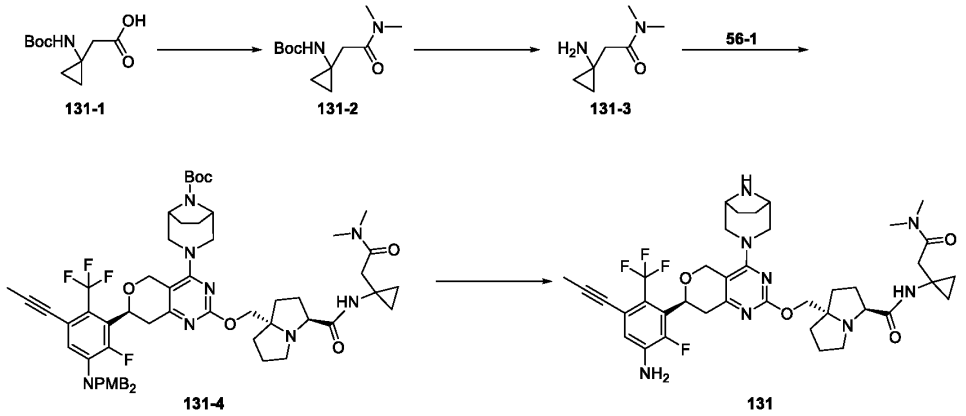
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **129-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-80%) to afford compound **129**. MS m/z = 778.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.68 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.08 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.82 - 3.75 (m, 4H), 3.52 - 3.45 (m, 5H), 3.11 - 3.04 (m, 1H), 2.93 (d, *J* = 12.0 Hz, 1H), 2.79 - 2.70 (m, 2H), 2.43 - 2.35 (m, 1H), 2.21 - 2.16 (m, 2H), 2.01 - 1.99 (m, 5H), 1.94 - 1.88 (m, 2H), 1.82 - 1.71 (m, 4H), 1.60 (d, *J* = 12.0 Hz, 1H).

Example 130



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **130-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xtimate C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **130**. MS m/z = 746.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.15 (t, *J* = 12.0 Hz, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.79 - 3.75 (m, 1H), 3.62 - 3.58 (m, 2H), 3.58 - 3.49 (m, 7H), 3.48 - 3.40 (m, 2H), 3.39 - 3.34 (m, 4H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.98 - 2.92 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.77 - 2.71 (m, 1H), 2.16 - 2.09 (m, 2H), 2.05 - 1.98 (m, 5H), 1.96 - 1.81 (m, 6H), 1.77 - 1.67 (m, 2H).

Example 131



Step 1

To a stirred solution of compound **131-1** (85 mg, 394.90 μmol) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (153.12 mg, 1184.70 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (330.30 mg, 789.80 μmol) and dimethylamine hydrochloride (35.61 mg，789.80 μmol). The reaction was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by reverse Flash Spherical C18 (ACN-H_2O (0.1% FA); Gradient: (ACN): 10%-40%) to afford compound **131-2**. MS m/z = 243.2 $[M+H]^+$.

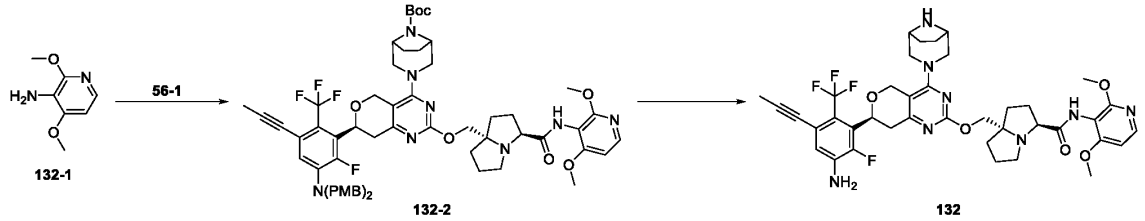
Step 2

A mixture of compound **131-2** (45 mg, 185.71 μmol) and HCl (1.0 mL, 2.5 M) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure to afford compound **131-3** as HCl salt. MS m/z = 143.2 $[M+H]^+$.

Step 3

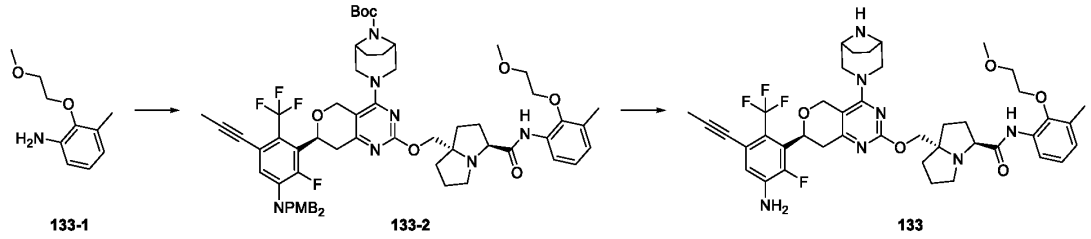
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **131-3** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 10%-40%) to afford compound **131**. MS m/z = 769.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.14 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 8.0 Hz, 2H), 4.03 (d, J = 12.0 Hz, 1H), 3.72 - 3.62 (m, 1H), 3.52 (d, J = 12.0 Hz, 3H), 3.41 (d, J = 12.0 Hz, 1H), 3.21 (dd, J = 16.0, 8.0 Hz, 1H), 3.06 - 3.01 (m, 4H), 2.91 (s, 3H), 2.88 - 2.78 (m, 3H), 2.73 - 2.63 (m, 2H), 2.13 - 1.98 (m, 6H), 1.97 - 1.80 (m, 7H), 1.75 - 1.65 (m, 2H), 0.80 (s, 4H).

Example 132



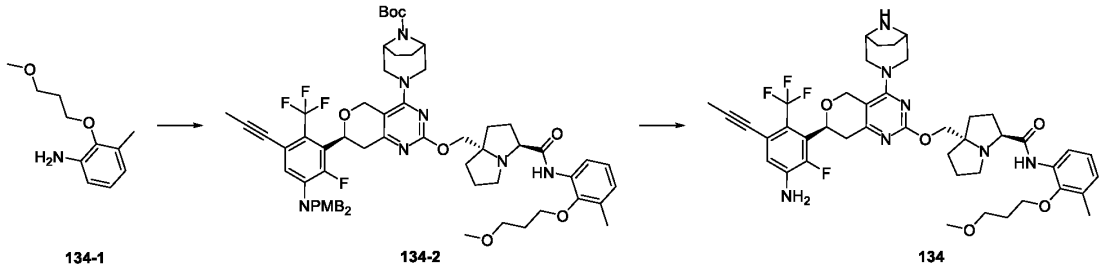
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **132-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 10%-40%) to afford compound **132**. MS m/z = 781.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.99 (d, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.81 - 4.79 (m, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.22 (d, *J* = 8.0 Hz, 1H), 4.11 (d, *J* = 8.0 Hz, 1H), 4.05 - 4.01 (m, 1H), 3.90 (d, *J* = 12.0 Hz, 6H), 3.69 - 3.64 (m, 2H), 3.58 (d, *J* = 12.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.28 - 3.16 (m, 2H), 3.15 - 3.06 (m, 2H), 2.98 - 2.92 (m, 1H), 2.87 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.24 - 2.16 (m, 2H), 2.14 - 2.04 (m, 4H), 2.01 (s, 3H), 1.93 - 1.86 (m, 3H), 1.82 - 1.74 (m, 3H).

Example 133



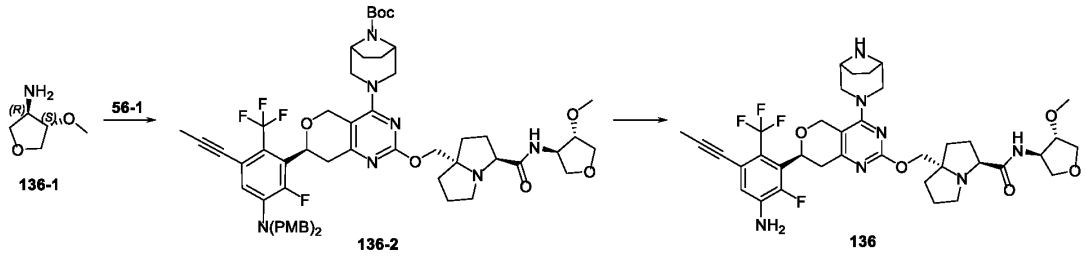
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **133-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **133**. MS m/z = 808.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.02 - 6.89 (m, 3H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.10 (m, 3H), 4.09 - 4.04 (m, 1H), 4.00 - 3.92 (m, 2H), 3.71 - 3.68 (m, 2H), 3.60 - 3.54 (m, 3H), 3.48 (s, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.18 (m, 1H), 3.08 - 2.98 (m, 2H), 2.88 - 2.82 (m, 2H), 2.30 (s, 3H), 2.24 - 2.10 (m, 4H), 2.04 - 1.99 (m, 6H), 1.94 - 1.85 (m, 3H), 1.82 - 1.70 (m, 2H).

Example 134



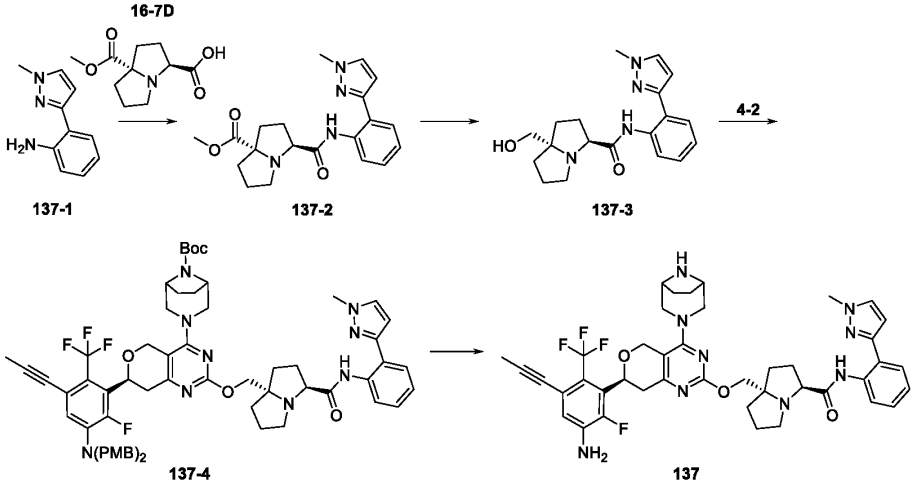
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **134-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-68%) to afford compound **134**. MS m/z = 822.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.01 - 6.97 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 8.0 Hz, 1H), 4.16 - 4.09 (m, 2H), 4.04 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.90 - 3.87 (m, 2H), 3.67 - 3.52 (m, 5H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.34 (s, 3H), 3.24 - 3.19 (m, 1H), 3.08 - 2.99 (m, 2H), 2.89 - 2.79 (m, 2H), 2.29 (s, 3H), 2.24 - 2.08 (m, 4H), 2.06 - 2.02 (m, 6H), 1.99 - 1.91 (m, 3H), 1.85 - 1.74 (m, 4H).

Example 136



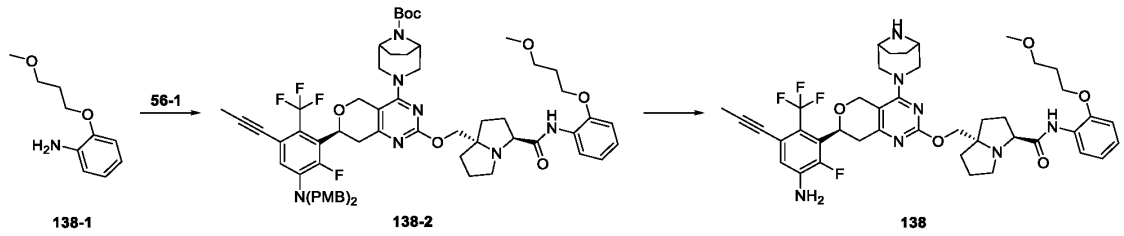
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **136-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **136**. MS m/z = 744.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.32 - 4.30 (m, 1H), 4.15 (t, *J* = 12.0 Hz, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 4.00 - 3.95 (m, 2H), 3.84 - 3.82 (m, 1H), 3.78 - 3.70 (m, 2H), 3.66 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.56 - 3.52 (m, 3H), 3.44 - 3.42 (m, 4H), 3.25 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.91 - 2.82 (m, 2H), 2.79 - 2.73 (m, 1H), 2.15 - 2.07 (m, 2H), 2.05 - 1.96 (m, 5H), 1.95 - 1.80 (m, 6H), 1.77 - 1.66 (m, 2H).

Example 137



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **137-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **137**. MS m/z = 800.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.0, 4.0 Hz, 1H), 7.56 (d, J = 4.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 4.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 4.0 Hz, 1H), 5.08 (dd, J = 12.0, 4.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 8.0 Hz, 1H), 4.09 (d, J = 12.0 Hz, 1H), 3.99 (s, 3H), 3.93 (d, J = 16.0 Hz, 1H), 3.51 (t, J = 4.0 Hz, 1H), 3.46 - 3.35 (m, 4H), 3.22 (d, J = 16.0 Hz, 1H), 3.11 (dd, J = 20.0, 12.0 Hz, 1H), 2.85 (d, J = 12.0 Hz, 1H), 2.81 - 2.71 (m, 2H), 2.37 - 2.30 (m, 1H), 2.25 - 2.18 (m, 1H), 2.06 - 1.97 (m, 7H), 1.88 - 1.70 (m, 5H), 1.61 - 1.55 (m, 1H).

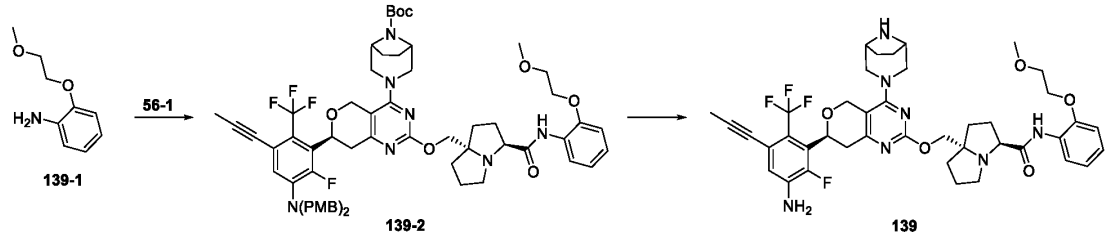
Example 138



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **138-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O

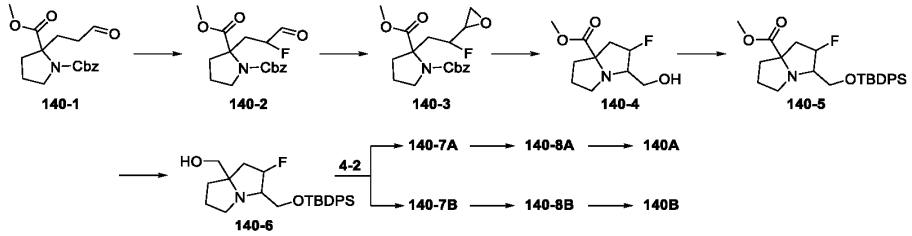
(0.1% NH_3); Gradient: (ACN): 33%-62%) to afford compound **138**. MS m/z = 808.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.92 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.13 - 7.08 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.94 - 6.89 (m, 2H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.17 - 4.10 (m, 4H), 4.05 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.66 - 3.53 (m, 5H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.33 (s, 3H), 3.23 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.08 - 3.05 (m, 2H), 2.89 - 2.78 (m, 2H), 2.24 - 2.13 (m, 2H), 2.10 - 1.86 (m, 13H), 1.80 - 1.70 (m, 2H).

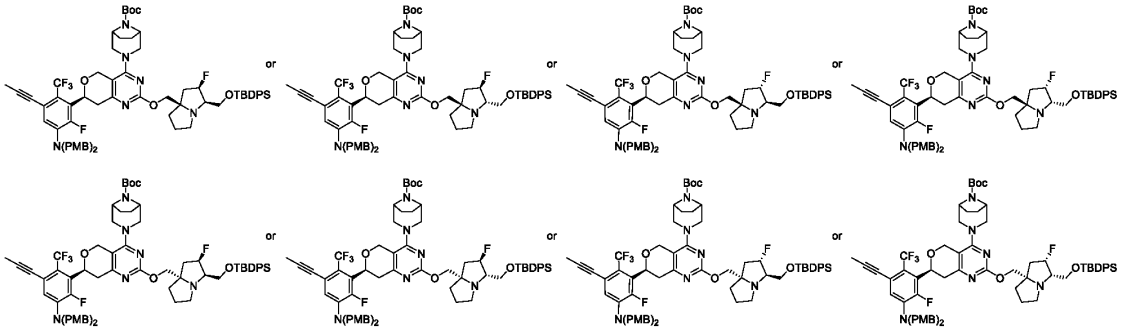
Example 139



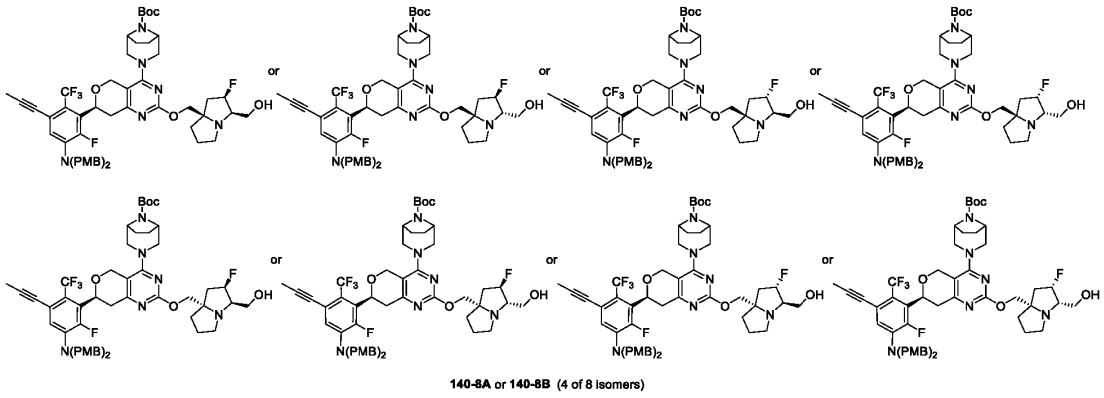
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **139-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **139**. MS m/z = 794.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.12 - 7.08 (m, 1H), 7.05 - 7.02 (m, 1H), 6.97 - 6.93 (m, 1H), 6.91 - 6.88 (m, 1H), 5.15 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 13.6 Hz, 1H), 4.23 - 4.16 (m, 3H), 4.14 - 4.09 (m, 2H), 4.04 - 4.00 (m, 1H), 3.77 - 3.74 (m, 2H), 3.55 - 3.52 (m, 3H), 3.45 - 3.43 (m, 1H), 3.42 (s, 3H), 3.25 - 3.18 (m, 1H), 3.10 - 3.02 (m, 2H), 2.88 - 2.77 (m, 2H), 2.23 - 2.08 (m, 4H), 2.01 (s, 3H), 1.99 - 1.93 (m, 4H), 1.85 - 1.80 (m, 2H), 1.78 - 1.69 (m, 2H).

Example 140

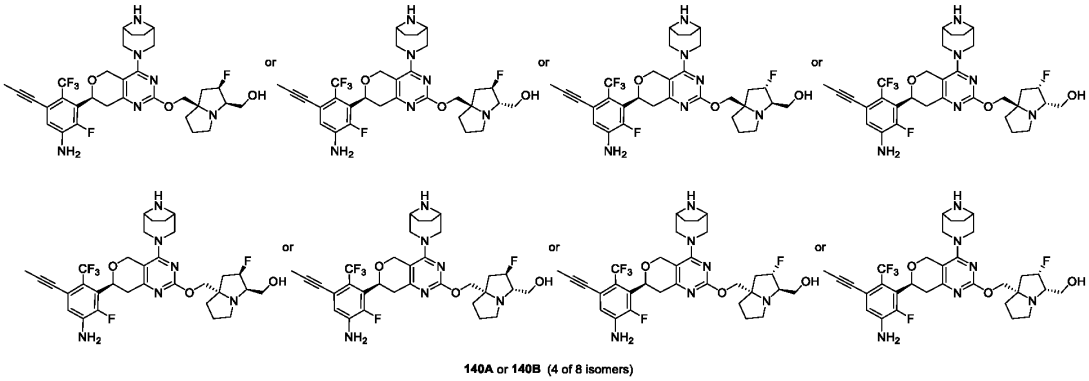




140-7A or 140-7B (4 of 8 isomers)



140-8A or 140-8B (4 of 8 isomers)



140A or 140B (4 of 8 isomers)

Step 1

To a stirred solution of compound **140-1** (1.1 g, 3.44 mmol) in DCM (3 mL) was added triethyl amine (1.05 g, 10.33 mmol) and trimethylsilyl trifluoromethanesulfonate (1.53 g, 6.89 mmol) at 0 °C. The mixture was stirred at 25 °C for 3 hours. The reaction was quenched with water (10 mL), extracted wtih PE (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was redissolved in acetonitrile (20 mL), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.83 g, 5.17 mmol) was added and the mixture was stirred at 25 °C for 12 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over

anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **140-2.** MS m/z = 338.3 $[M+H]^+$.

Step 2

Sodium hydride (70.43 mg, 2.93 mmol, 60% purity) was added in dry DMSO (8 mL) at 0 °C and the mixture was stirred at 55 °C for 2 hours. Then trimethylsulfoxonium iodide (587.13 mg, 2.67 mmol) was added, and the resulting mixture was stirred at 25 °C for 15 minutes. After that, compound **140-2** (450 mg, 1.33 mmol) was added. The reaction was stirred at 25 °C for another 2 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **140-3.** MS m/z = 352.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **140-3** (400 mg, 1.14 mmol) in MeOH (5 mL) was added Pd/C (121.15 mg, 1.14 mmol, 10% purity) and the mixture was stirred at 25 °C for 12 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was concentrated under reduced pressure to afford compound **140-4**. MS m/z = 218.2 $[M+H]^+$.

Step 4

To a stirred solution of compound **140-4** (210 mg, 966.69 μmol) in DCM (4 mL) was added imidazole (65.81 mg, 966.69 μmol) and tert-butylchlorodiphenylsilane (265.70 mg, 966.69 μmol) at 0 °C. The reaction was stirred at 25 °C for 3 hours. The reaction was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc = 10:1) to afford compound **140-5**. MS m/z = 456.3 $[M+H]^+$.

Step 5

To a stirred solution of compound **140-5** (200 mg, 438.95 μmol) in dry THF (4 mL) was added lithium aluminum hydride (658.4 μL, 658.42 μmol, 1 M in THF) at 0 °C. The reaction was stirred at 25 °C for 0.5 hours. The reaction was quenched with water (2 mL), extracted wtih DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc = 2:1) to afford compound **140-6**. MS m/z = 428.3 $[M+H]^+$.

Step 6

To a stirred solution of compound **140-6** (61.73 mg, 70.15 μmol) in dry N,N-dimethylformamide (2 mL) was added sodium hydride (2.53 mg, 105.23 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 45 minutes. Then compound **4-2** (30 mg, 70.15 μmol) was added, and the reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (2 mL), extracted wtih DCM

(3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc = 3:1) to afford compound **140-7A** (mixture) and **140-7B** (mixture). compound **140-7A** (mixture) (PE:EtOAc = 3:1, Rf = 0.6), MS m/z = 1227.9 $[M+H]^+$; compound **140-7B** (mixture) (PE:EtOAc = 3:1, Rf = 0.4), MS m/z = 1227.9 $[M+H]^+$.

Step 7

To a stirred solution of compound **140-7A** (23 mg, 18.74 μmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.1 mL, 100 μmol, 1 M in THF) and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with water (2 mL), extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford compound **140-8A** (mixture). MS m/z = 989.7 $[M+H]^+$.

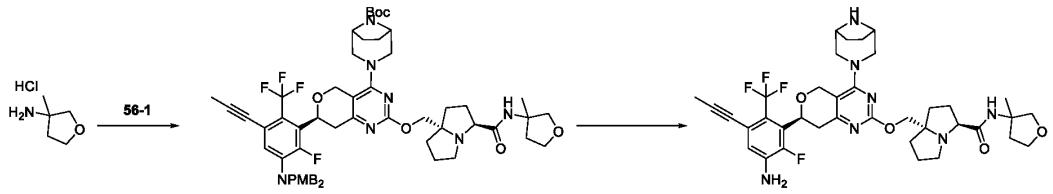
With reference to step 7, compound **140-7A** was replaced with compound **140-7B** as the raw material to obtain compound **140-8B** (mixture). MS m/z = 989.7 $[M+H]^+$.

Step 8

To a solution of compound **140-8A** (17 mg, 17.19 μmol) in DCM (1.2 mL) was added TFA (0.3 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Sunfire-C18, 19 x 250mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 12%-30%) to afford compound **140A** (mixture) as FA salt. MS m/z = 649.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.47 (s, 1.69H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.31 (dt, *J* = 52.0, 4.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.80 (m, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.30 - 4.17 (m, 3H), 4.06 (d, *J* = 4.0 Hz, 2H), 3.85 - 3.80 (m, 1H), 3.75 (d, *J* = 12.0 Hz, 1H), 3.69 - 3.60 (m, 2H), 3.30 - 3.23 (m, 2H), 3.15 - 3.04 (m, 2H), 2.97 - 2.86 (m, 2H), 2.56 - 2.46 (m, 1H), 2.29 - 2.22 (m, 1H), 2.10 - 2.04 (m, 3H), 2.03 - 1,99 (m, 4H), 1.97 - 1.90 (m, 3H), 1.86 - 1.81 (m, 1H).

To a solution of compound **140-8B** (18 mg, 18.20 μmol) in DCM (1.2 mL) was added TFA (0.3 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Sunfire-C18, 19 x 250mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 12%-30%) to afford compound **140B** (mixture) as FA salt. MS m/z = 649.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.48 (s, 1.10H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.80 (m, 1H), 4.73 - 4.69 (m, 1H), 4.63 - 4.48 (m, 1H), 4.46 - 4.31 (m, 1H), 4.30 - 4.18 (m, 2H), 4.08 - 4.02 (m, 2H) , 3.95 - 3.82 (m, 1H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.63 - 3.57 (m, 1H), 3.28 - 3.22 (m, 2H), 3.15 - 3.09 (m, 3H), 2.94 - 2.81 (m, 2H), 2.30 - 2.21 (m, 2H), 2.12 - 1.84 (m, 10H), 1.72 - 1.64 (m, 1H).

Example 141



141-1 141-2 141

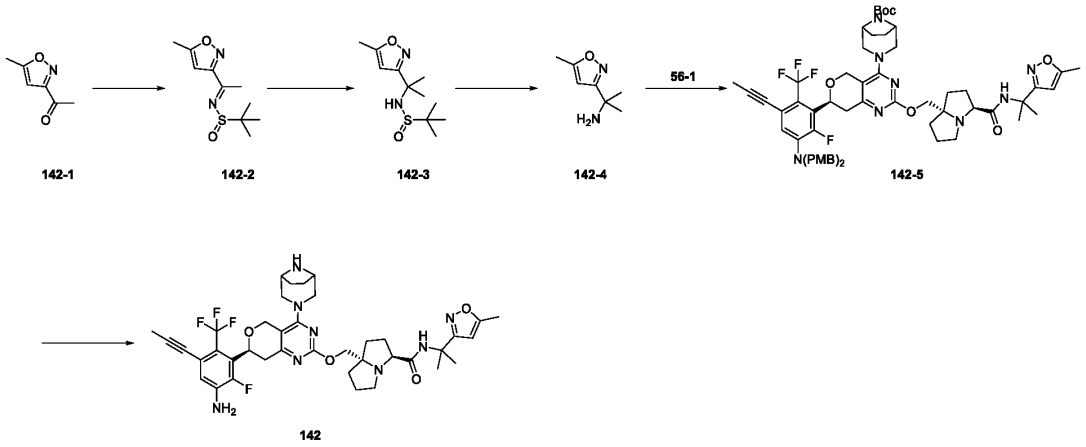
Step 1

To a stirred solution of compound **56-1** (90 mg, 101.15 μmol) in N,N-dimethylformamide (2.5 mL) was added N,N-diisopropylethylamine (70.72 mg, 548.22 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (69.44 mg, 182.74 μmol) and compound **141-1** (30.80 mg, 304.55 μmol). The mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **141-2**. MS m/z = 1068.7 $[M+H]^+$.

Step 2

The mixture of compound **141-2** (0.10 g, 0.098 mmol) in TFA (2.5 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 5%-50%) to afford compound **141**. MS m/z = 728.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.83 - 4.78 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.06 - 3.96 (m, 2H), 3.93 - 3.88 (m, 2H), 3.75 - 3.72 (m, 1H), 3.66 - 3.62 (m, 1H), 3.54 - 3.51 (m, 3H), 3.43 - 3.40 (m, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.94 - 2.91 (m, 1H), 2.87 - 2.82 (m, 1H), 2.77 - 2.72 (m, 1H), 2.32 - 2.26 (m, 1H), 2.13 - 2.07 (m, 2H), 2.04 - 2.00 (m, 4H), 1.95 - 1.88 (m, 6H), 1.85 - 1.83 (m, 2H), 1.75 - 1.69 (m, 2H), 1.48 (s, 3H).

Example 142



Step 1

To a stirred solution of compound **142-1** (500 mg, 4.0 mmol) in THF (5 mL) was added titanium tetraisopropanolate (2.27 g, 8.0 mmol) and tert-butanesulfinamide (581 mg, 4.8 mmol). The reaction was stirred at 70 °C for 4 hours. The reaction was quenched with water (1 mL), filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **142-2**. MS m/z = 229.1 $[M+H]^+$.

Step 2

To a stirred solution of compound **142-2** (400 mg, 1.75 mmol) in dry THF (5 mL) was added methylmagnesium bromide (1.75 mL, 5.26 mmol, 3.0 M in THF) at -78 °C under nitrogen atmosphere and the mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water (0.2 mL), extracted wtih EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **142-3**. MS m/z = 245.2 $[M+H]^+$.

Step 3

To a stirred solution of compound **142-3** (100 mg, 0.49 mmol) in DCM (2 mL) was added HCl (1 mL, 4 M in EtOAc) and the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure to afford compound **142-4** as HCl salt. MS m/z = 141.2 $[M+H]^+$.

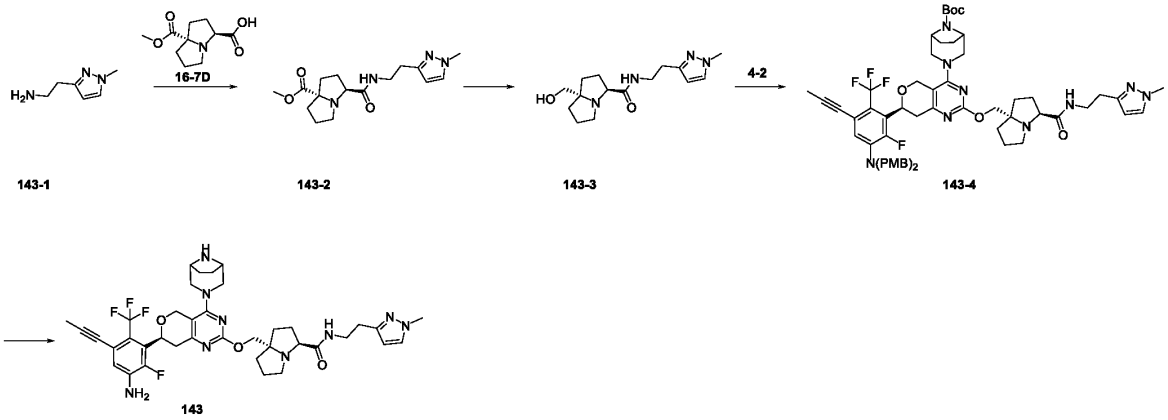
Step 4

To a stirred solution of compound **56-1** (50 mg, 50.76 μmol) in acetonitrile (2 mL) was added N methylimidazole (12.5 mg, 152.28 μmol), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (21.4 mg, 76.14 μmol) and compound **142-4** (14.2 mg, HCl salt). The mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:5) to afford compound **142-5**. MS m/z = 1107.8 $[M+H]^+$.

Step 5

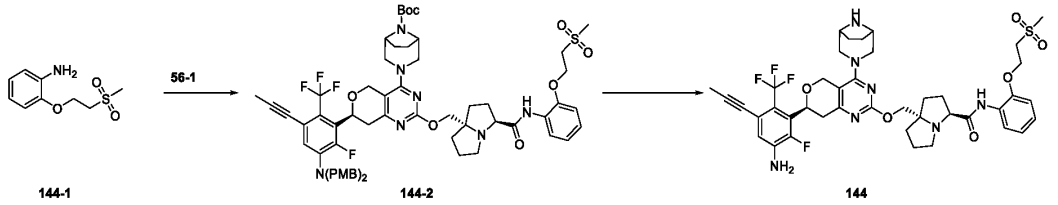
To a solution of compound **142-5** (30 mg, 27.09 μmol) in DCM (2 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **142**. MS m/z = 767.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 1H), 5.25 - 5.12 (m, 1H), 4.83 - 4.76 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.84 - 3.76 (m, 1H), 3.70 - 3.65 (m, 1H), 3.61 - 3.50 (m, 3H), 3.48 - 3.40 (m, 1H), 3.28 - 3.17 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.66 (m, 3H), 2.37 (s, 3H), 2.15 - 1.79 (m, 12H), 1.78 - 1.68 (m, 2H), 1.66 (s, 3H), 1.62 (s, 3H).

Example 143



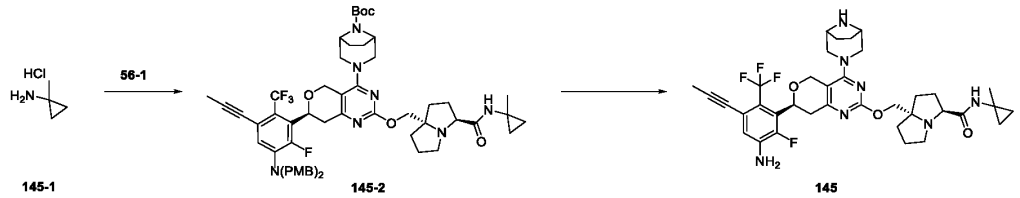
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **143-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **143**. MS m/z = 752.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.46 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 5.18 - 5.14 (m, 1H), 4.80 - 4.77 (m, 1H), 4.68 (d, *J* = 12.0 Hz, 1H),4.23 - 4.07 (m, 4H), 3.81 (s, 3H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.56 - 3.44 (m, 4H), 3.28 - 3.11 (m, 2H), 3.01 - 2.72 (m, 6H), 2.22 - 2.05 (m, 5H), 2.02 (s, 3H), 1.99 - 1.90 (m, 4H), 1.88 - 1.70 (m, 3H).

Example 144



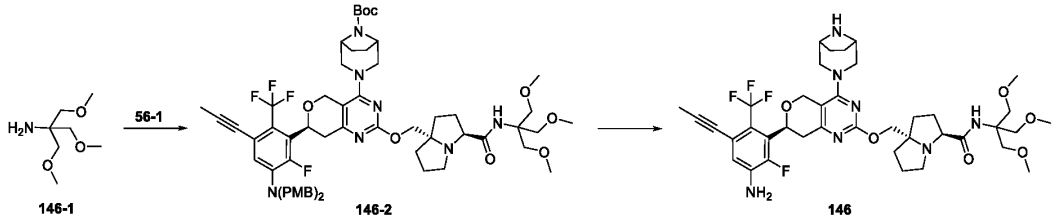
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **144-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **144**. MS m/z = 842.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.06 (d, *J* = 8.0 Hz, 1H), 7.16 - 7.09 (m, 2H), 7.02 - 6.98 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.14 (m, 1H), 4.81 - 4.78 (m, 1H), 4.68 - 4.64 (m, 1H), 4.54 - 4.50 (m, 2H), 4.22 - 4.08 (m, 3H), 4.02 - 3.98 (m, 1H), 3.66 - 3.63 (m, 2H), 3.62 - 3.60 (m, 1H), 3.56 - 3.53 (m, 2H), 3.45 - 3.42 (m, 2H), 3.27 - 3.19 (m, 1H), 3.08 (s, 3H), 3.00 - 2.96 (m, 1H), 2.89 - 2.77 (m, 2H), 2.25 - 2.05 (m, 4H), 2.04 - 1.99 (m, 4H), 1.98 - 1.84 (m, 5H), 1.80 - 1.68 (m, 2H).

Example 145



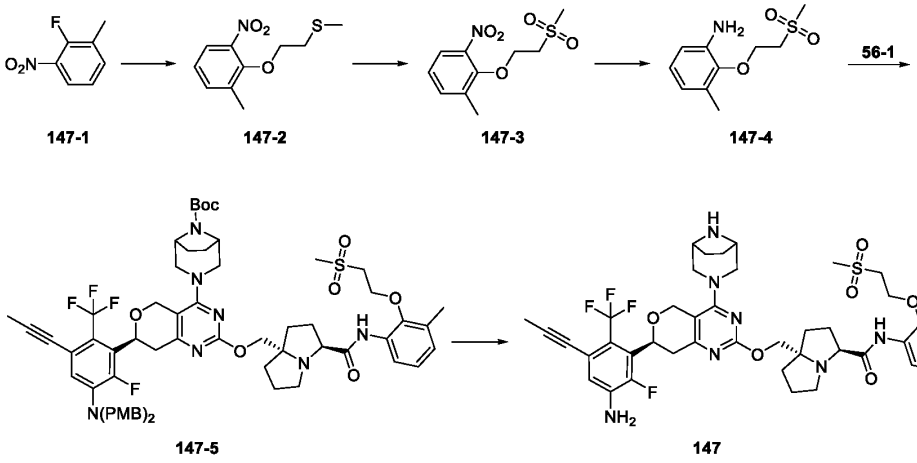
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **145-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **145**. MS m/z = 698.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 - 5.13 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.04 (d, *J* = 8.0 Hz, 1H), 3.65 - 3.63 (m, 1H), 3.55 - 3.51 (m, 3H), 3.44 - 3.41 (m, 1H), 3.22 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.87 - 2.86 (m, 2H), 2.77 - 2.71 (m, 1H), 2.12 - 2.05 (m, 2H), 2.01 (s, 3H), 1.97 - 1.89 (m, 5H), 1.86 - 1.82 (m, 3H), 1.74 - 1.67 (m, 2H), 1.35 (s, 3H), 0.73 - 0.69 (m, 2H), 0.66 - 0.60 (m, 2H).

Example 146



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **146-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_4HCO_3); Gradient: (ACN): 35%-75%) to afford compound **146**. MS m/z = 790.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.17 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.01 (s, 2H), 5.02 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 3.94 - 3.89 (m, 2H), 3.83 (d, J = 8.0 Hz, 1H), 3.61 (t, J = 4.0 Hz, 1H), 3.54 (s, 6H), 3.44 (s, 2H), 3.36 - 3.32 (m, 2H), 3.27 (s, 1H), 3.23 (s, 9H), 3.07 - 3.00 (m, 1H), 2.88 (d, J = 12.0 Hz, 1H), 2.82 - 2.71 (m, 3H), 2.03 (s, 3H), 1.88 - 1.81 (m, 6H), 1.77-1.72 (m, 3H), 1.62 - 1.55 (m, 3H).

Example 147



Step 1

To a stirred solution of 2-methylthioethanol (500 mg, 5.43 mmol) in N,N-dimethylformamide (10 mL) was added potassium carbonate (2.25 g, 16.28 mmol) and compound **147-1** (841.62 mg, 5.43 mmol). The mixture was stirred at 50 °C for 12 hours. The reaction was quenched with water (10 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 4:1) to afford compound **147-2**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.70 (dd, J = 8.0, 4.0 Hz, 1H), 7.58 (d, J = 4.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 4.09 (t, J =

4.0 Hz, 2H), 2.84 (t, *J* = 4.0 Hz, 2H), 2.36 (s, 3H), 2.13 (s, 3H).

Step 2

To a stirred solution of compound **147-2** (600 mg, 2.64 mmol) in DCM (10 mL) was added 3-chloroperoxybenzoic acid (1.37 g, 7.92 mmol) and the mixture was stirred at 25 °C for 2 hours. The reaction was quenched with saturated solution of sodium sulfite (20 mL), extracted wtih EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 2:1) to afford compound **147-3**. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 4.31 (t, *J* = 4.0 Hz, 2H), 3.64 (t, *J* = 4.0 Hz, 2H), 3.08 (s, 3H), 2.37 (s, 3H).

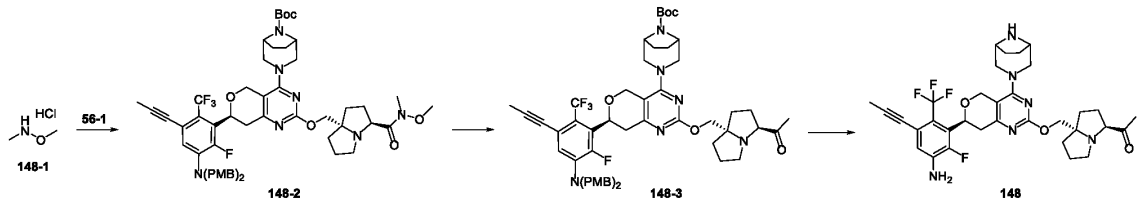
Step 3

To a stirred solution of compound **147-3** (300 mg, 1.16 mmol) in MeOH (10 mL) was added Pd/C (12.31 mg, 10% purity) and the mixture was stirred at 25 °C for 2 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **147-4**. MS m/z = 230.1 $[M+H]^+$.

Step 4

With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **147-4** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-70%) to afford compound **147**. MS m/z = 856.6 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.94 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.07 - 6.99 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.79 (s, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.24 - 4.08 (m, 6H), 3.74 - 3.67 (m, 1H), 3.66 - 3.55 (m, 4H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.27 - 3.20 (m, 1H), 3.16 (s, 3H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.94 (m, 1H), 2.88 - 2.82 (m, 2H), 2.34 (s, 3H), 2.25 - 2.09 (m, 4H), 2.04 - 1.94 (m, 7H), 1.90 - 1.84 (m, 2H), 1.81 - 1.73 (m, 2H).

Example 148



Step 1

To a stirred solution of compound **56-1** (50 mg, 0.05 mmol) in DCM (4 mL) was added N,N-diisopropylethylamine (16 mg, 0.13 mmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (25 mg, 0.07 mmol) and compound **148-1** (6 mg, 0.06 mmol). The reaction was stirred at 25 °C for 6 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **148-2**. MS m/z = 1028.7 $[M+H]^+$.

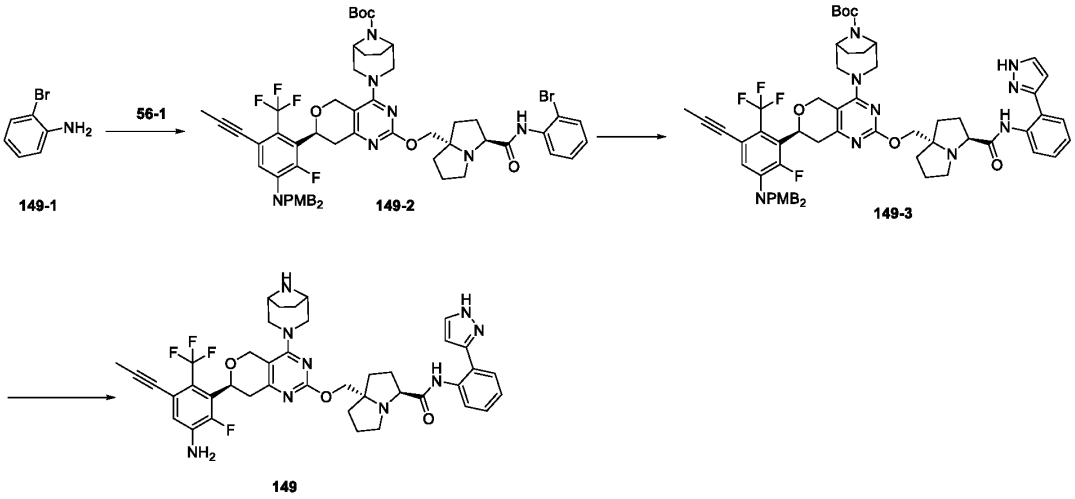
Step 2

To a stirred solution of compound **148-2** (30 mg, 28.19 μmol) in dry THF (2 mL) was added methylmagnesium bromide (58 μL, 145 μmol, 2.5 M in THF) at 0 °C under nitrogen atmosphere and the mixture was stirred at 25 °C for 1 hour. The reaction was quenched with saturated NH_4Cl solution (1 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 20:1) to afford compound **148-3**. MS m/z = 983.7 $[M+H]^+$.

Step 3

To a solution of compound **148-3** (20 mg, 20.34 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-60%) to afford compound **148**. MS m/z = 643.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.77 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.10 (m, 3H), 3.58 - 3.52 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 2H), 3.20 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.10 - 3.04 (m, 2H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.68 - 2.62 (m, 1H), 2.17 - 2.13 (m, 5H), 2.05 - 2.01 (m, 5H), 1.96 - 1.85 (m, 5H), 1.73 - 1.69 (m, 3H).

Example 149



Step 1

To a stirred solution of compound **56-1** (60 mg, 60.91 μmol) in dry acetonitrile (2 mL) was added chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (20.51 mg, 73.09 μmol), compound **149-1** (20.96 mg, 121.82 μmol) and N-methylimidazole (17.50 mg, 213.18 mmol). The mixture was stirred at 25 °C for 12 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **149-2**. MS m/z =1138.7 $[M+H]^+$.

Step 2

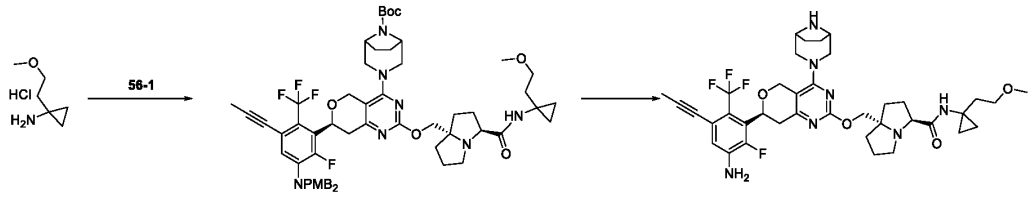
To a stirred solution of compound **149-2** (30 mg, 26.34 μmol) in 1,4-dioxane (0.25 mL) and water (1 mL) was added cesium carbonate (25.74 mg, 79.01 μmol), pyrazole-3-boronic acid (8.84 mg, 79.01) and methanesulfonato(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II) (4.46 mg, 5.27 μmol). The mixture was stirred at 60 °C for 2 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **149-3**. MS m/z = 1126.6 $[M+H]^+$.

Step 3

To a solution of compound **149-3** (15 mg, 13.32 μmol) in DCM (0.5 mL) was added TFA (0.5 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **149**. MS m/z = 786.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.54 (d, *J* = 8.0 Hz, 1H), 7.73 - 7.59 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.66 - 6.57 (m, 1H), 5.13 - 5.04 (m, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H),

4.09 (d, J = 8.0 Hz, 1H), 3.95 (d, J = 12.0 Hz, 1H), 3.48 - 3.38 (m, 3H), 3.26 - 3.17 (m, 2H), 3.15 - 3.10 (m, 1H), 2.90 - 2.84 (m, 1H), 2.81 - 2.74 (m, 1H), 2.71 - 2.65 (m, 1H), 2.42 - 2.36 (m, 1H), 2.19 - 2.09 (m, 3H), 2.01 (s, 3H), 1.97 - 1.89 (m, 2H), 1.87 - 1.80 (m, 2H), 1.76 - 1.69 (m, 3H), 1.62 - 1.54 (m, 2H).

Example 150



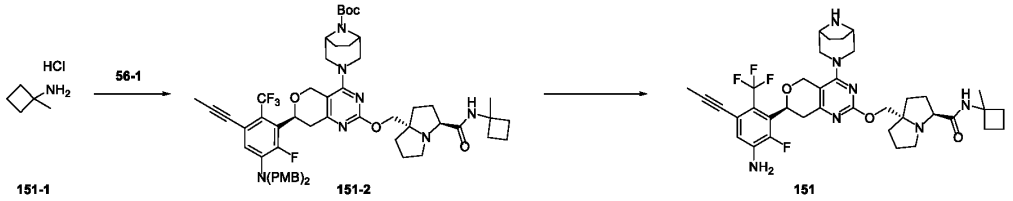
Step 1

To a stirred solution of compound **56-1** (50 mg, 50.76 μmol) in DCM (2.0 mL) was added N,N-diisopropylethylamine (19.68 mg, 152.27 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (38.60 mg, 101.52 μmol) and compound **150-1** (11.69 mg, 101.52 μmol). The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 0:1) to afford compound **150-2**. MS m/z = 1082.8 $[M+H]^+$.

Step 2

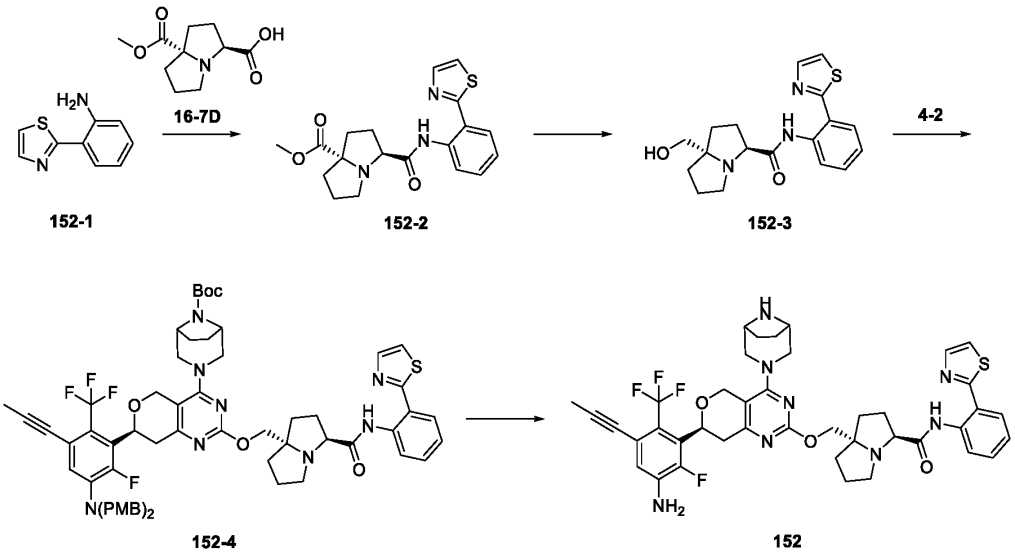
To a solution of compound **150-2** (50 mg, 46.20 μmol) in DCM (1 mL) was added TFA (1 mL), the mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **150**. MS m/z = 742.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.19 - 5.11 (m, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.18 - 4.10 (m, 2H), 4.03 (d, J = 8.0 Hz, 1H), 3.69 - 3.63 (m, 1H), 3.58 - 3.48 (m, 5H), 3.45 - 3.39 (m, 1H), 3.30 (s, 3H), 3.26 - 3.17 (m, 1H), 3.08 - 3.00 (m, 1H), 2.91 - 2.80 (m, 2H), 2.79 - 2.70 (m, 1H), 2.13 - 2.05 (m, 2H), 2.04 - 1.95 (m, 5H), 1.94 - 1.78 (m, 8H), 1.77 - 1.68 (m, 2H), 0.76 - 0.64 (m, 4H).

Example 151



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **151-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **151**. MS m/z = 712.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.81 - 4.78 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.73 - 3.71 (m, 1H), 3.59 - 3.53 (m, 3H), 3.45 - 3.42 (m, 1H), 3.26 - 3.19 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.93 (m, 1H), 2.88 - 2.79 (m, 2H), 2.34 - 2.26 (m, 2H), 2.13 - 2.07 (m, 2H), 2.05 - 2.01 (m, 6H), 1.96 - 1.82 (m, 9H), 1.76 - 1.69 (m, 2H), 1.46 (s, 3H).

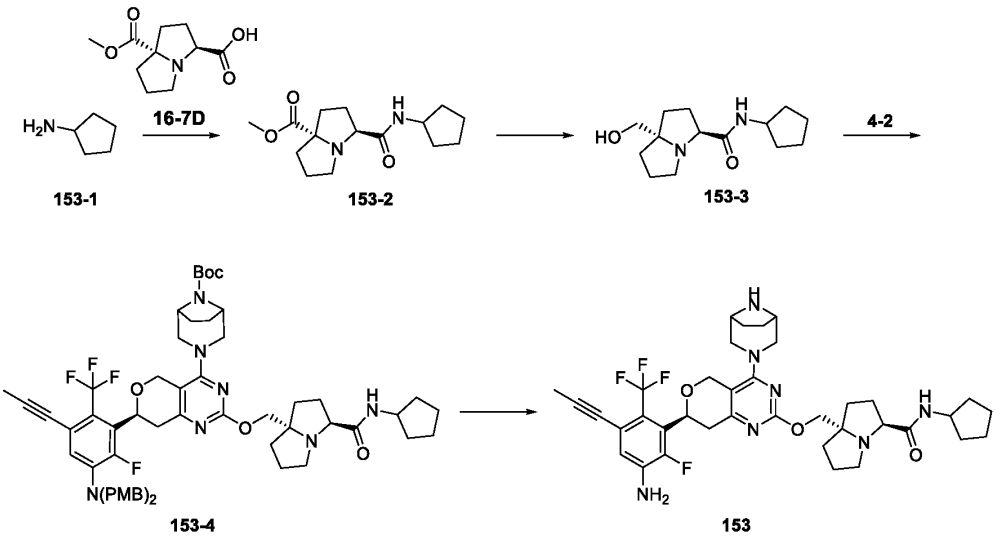
Example 152



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **152-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 25%-60%) to afford compound **152**. MS m/z = 803.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.60 (d, *J* = 8.0 Hz, 1H), 7.91 - 7.86 (m, 2H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 8.0 Hz, 1H), 4.17 - 4.09 (m, 3H), 3.60 - 3.54

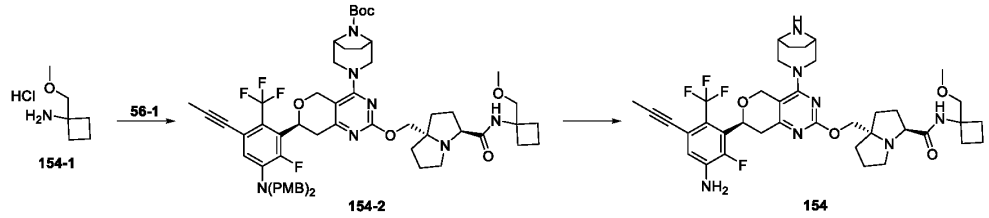
(m, 3H), 3.45 (d, J = 12.0 Hz, 1H), 3.27 - 3.20 (m, 1H), 3.07 - 3.04 (m, 2H), 2.87 (dd, J = 20.0, 4.0 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.26 - 2.16 (m, 3H), 2.07 - 2.02 (m, 5H), 1.91 - 1.67 (m, 7H).

Example 153



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **153-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-85%) to afford compound **153**. MS m/z = 712.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.18 - 4.10 (m, 3H), 4.05 (d, J = 8.0 Hz, 1H), 3.75 - 3.71 (m, 1H), 3.55 - 3.52 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.05 (d, J = 16.0 Hz, 1H), 2.92 - 2.82 (m, 2H), 2.78 - 2.72 (m, 1H), 2.13 - 2.08 (m, 2H), 2.04 - 1.89 (m, 11H), 1.86 - 1.84 (m, 2H), 1.77 - 1.59 (m, 6H), 1.53 - 1.45 (m, 2H).

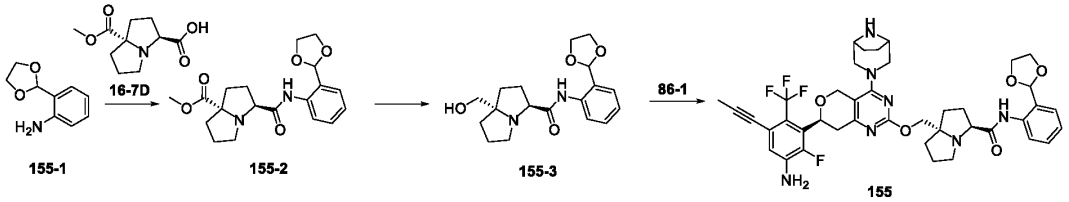
Example 154



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **154-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O

(0.1% NH_3); Gradient: (ACN): 50%-70%) to afford compound **154**. MS m/z = 742.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.13 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.73 (m, 1H), 3.63 - 3.52 (m, 5H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.36 (s, 3H), 3.22 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.97 (m, 1H), 2.88 - 2.74 (m, 2H), 2.30 - 2.01 (m, 10H), 1.97 - 1.80 (m, 9H), 1.76 - 1.68 (m, 2H).

Example 155



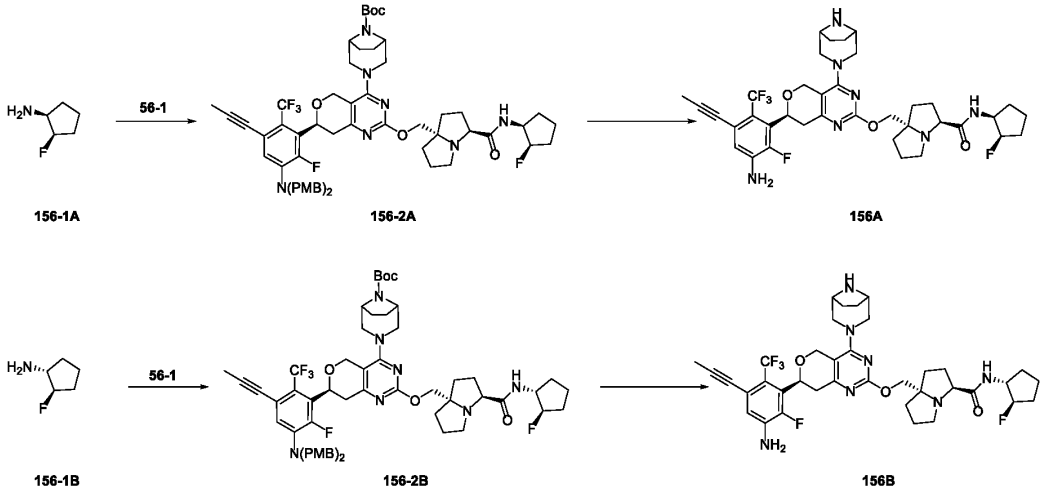
Step 1

With reference to steps 7~8 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **155-1** as the raw material to obtain compound **155-3**. MS m/z = 333.2 $[M+H]^+$.

Step 2

To a stirred solution of compound **155-3** (45 mg, 135.38 μmol) in dry THF (2 mL) was added sodium hydride (8.12 mg, 203.07 μmol, 60% purity) at 0 °C and the mixture was stirred at 25 °C for 0.5 hours. Then compound **86-1** (73.04 mg, 135.38 μmol) was added, and the reaction was stirred at 25 °C for 1.5 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge Prep C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-80%) to afford compound **155**. MS m/z = 792.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.96 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.79 (s, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.22 - 4.18 (m, 1H), 4.17 - 4.09 (m, 3H), 4.03 - 3.95 (m, 3H), 3.57 - 3.52 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.12 - 3.03 (m, 2H), 2.86 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.76 - 2.69 (m, 1H), 2.19 - 2.14 (m, 2H), 2.05 - 2.00 (m, 5H), 1.97 - 1.88 (m, 4H), 1.87 - 1.81 (m, 2H), 1.79 - 1.71 (m, 2H).

Example 156



Step 1

To a stirred solution of compound **56-1** (90 mg, 101.15 μmol) in N,N-dimethylformamide (2.5 mL) was added N,N-diisopropylethylamine (70.72 mg, 548.22 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (69.44 mg, 182.74 μmol) and compound **156-1A** (28.23 mg, 274.41 μmol). The mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **156-2A**. MS m/z =1070.7 $[M+H]^+$.

With reference to step 1, compound **156-1A** was replaced with compound **156-1B** as the raw material to obtain compound **156-2B**, MS m/z = 1070.7 $[M+H]^+$.

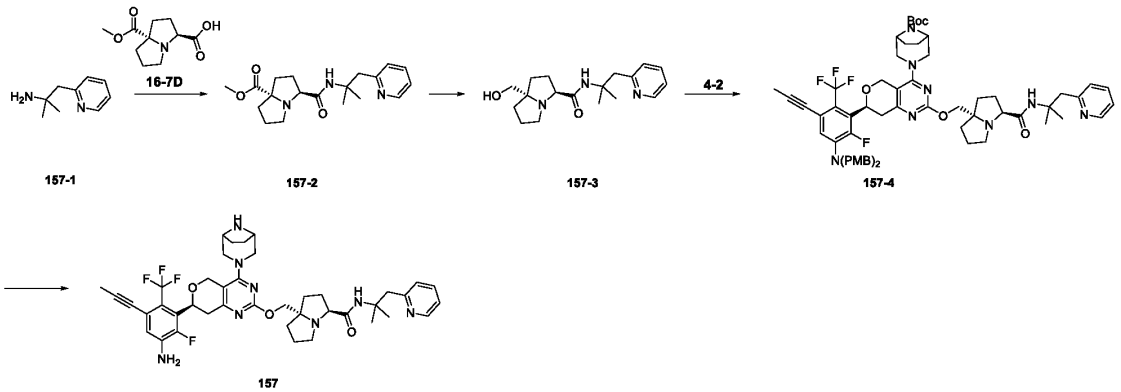
Step 2

The mixture of compound **156-2A** (60 mg, 56.07 μmol) in TFA (2 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 5%-50%) to afford compound **156A**. MS m/z = 730.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.09 (m, 1H), 4.93 - 4.77 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.27 - 4.11 (m, 3H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.77 - 3.71 (m, 1H), 3.57 - 3.47 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.91 - 2.80 (m, 2H), 2.77 - 2.69 (m, 1H), 2.17 - 2.06 (m, 3H), 2.03 - 1.96 (s, 5H), 1.96 - 1.77 (m, 10H), 1.76 - 1.64 (m, 2H), 1.59 - 1.50 (m, 1H).

The mixture of compound **156-2B** (50 mg, 46.69 μmol) in TFA (2 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 5%-50%) to afford compound **156B**. MS m/z = 730.5 $[M+H]^+$. ^1H NMR (400 MHz,

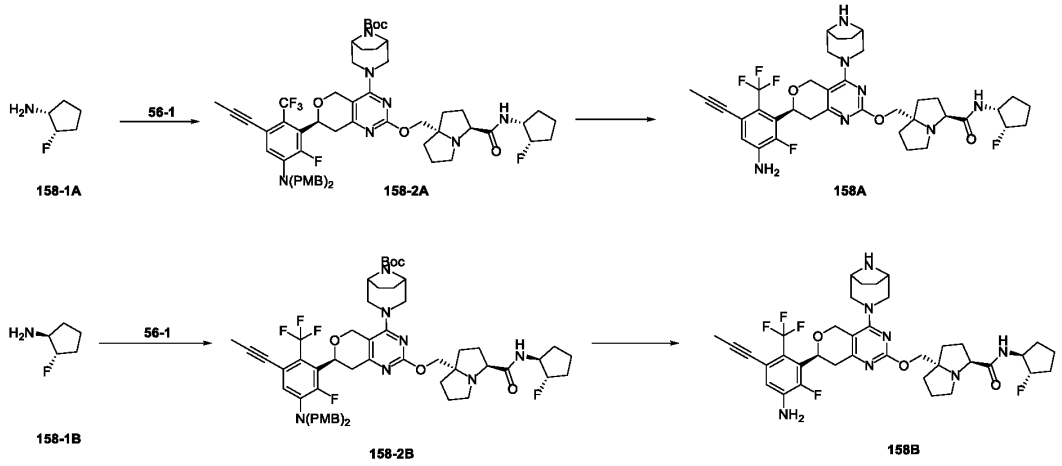
CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.11 (m, 1H), 4.94 - 4.78 (m, 2H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.26 - 4.11 (m, 3H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.55 - 3.47 (m, 3H), 3.45 - 3.37 (m, 1H), 3.25 - 3.17 (m, 1H), 3.03 (d, *J* = 12.0 Hz, 1H), 2.90 - 2.80 (m, 2H), 2.77 - 2.69 (m, 1H), 2.16 - 2.06 (m, 3H), 2.01 (s, 3H), 2.00 - 1.66 (m, 14H), 1.58 - 1.50 (m, 1H).

Example 157



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **157-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-60%) to afford compound **157**. MS m/z = 777.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.56 - 8.40 (m, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.35 - 7.18 (m, 2H)，6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 4.81 - 4.79 (m, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.29 - 4.16 (m, 3H), 4.10 (d, *J* = 12.0 Hz, 2H), 3.86 - 3.81 (m, 1H), 3.65 - 3.62 (m, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 3.37 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.18 (m, 1H), 3.16 – 3.09 (m, 1H), 3.03 (d, *J* = 12.0 Hz, 2H), 2.95 - 2.82 (m, 2H), 2.16 - 2.11 (m, 2H), 2.02 (s, 3H), 1.97 - 1.92 (m, 4H), 1.84 - 1.75 (m, 4H), 1.60 - 1.50 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H).

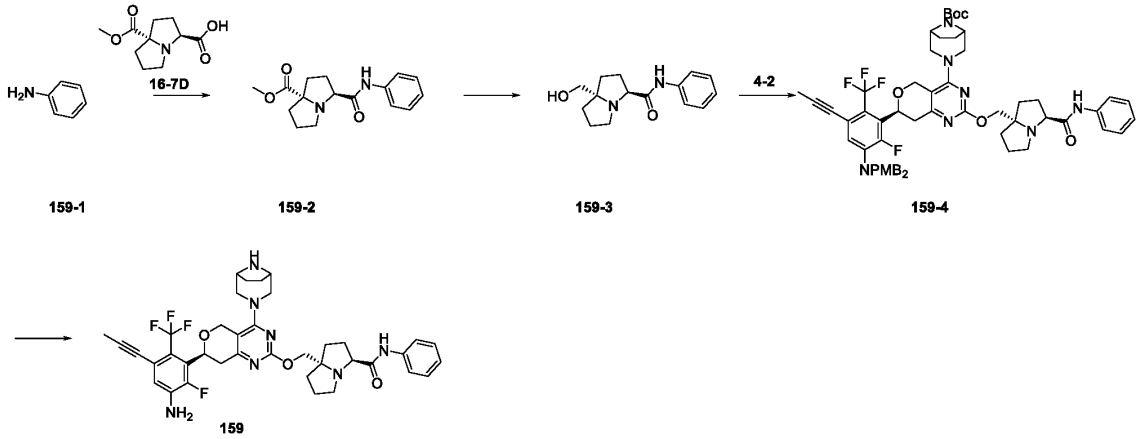
Example 158



With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **158-1A** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **158A**. MS m/z = 730.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.24 - 5.05 (m, 1H), 4.95 - 4.78 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.27 - 4.11 (m, 3H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.79 - 3.68 (m, 1H), 3.63 - 3.51 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.17 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.79 (m, 2H), 2.77 - 2.71 (m, 1H), 2.14 - 2.09 (m, 2H), 2.04 - 2.00 (m, 4H), 1.97 - 1.89 (m, 5H), 1.90 - 1.78 (m,6H), 1.80 - 1.70 (m, 2H), 1.63 - 1.45 (m, 2H).

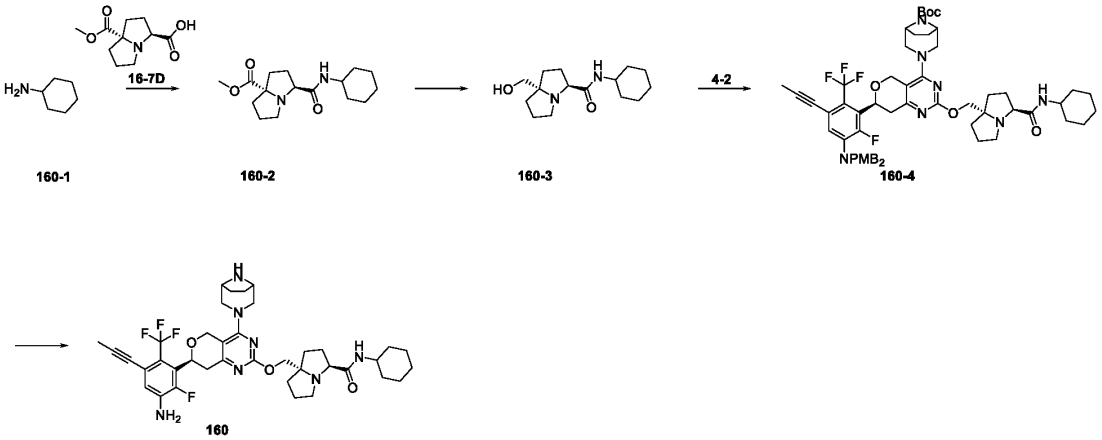
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **158-1B** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **158B**. MS m/z = 730.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, *J* = 8.0 Hz, 1H), 5.17 (d, *J* = 8.0 Hz, 1H), 4.95 - 4.78 (m, 2H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.36 - 4.11 (m, 3H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.60 - 3.53 (m, 3H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.28 - 3.17 (m, 1H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.81 (m, 2H), 2.79 - 2.71 (m, 1H), 2.23 - 2.08 (m, 3H), 2.06 - 1.99 (m, 5H), 1.98 - 1.92 (m, 5H), 1.89 - 1.79 (m,5H), 1.78 - 1.66 (m, 2H), 1.62 - 1.52 (m, 1H).

Example 159



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **159-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **159**. MS m/z = 720.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.59 - 7.56 (m, 2H), 7.33 - 7.29 (m, 2H), 7.12 - 7.08 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.23 - 4.08 (m, 3H), 3.96 - 3.93 (m, 1H), 3.57 - 3.52 (m, 3H), 3.45 - 3.42 (m, 1H), 3.27 - 3.20 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.98 - 2.93 (m, 1H), 2.89 - 2.80 (m, 2H), 2.26 - 2.13 (m, 1H), 2.16 - 2.02 (m, 2H), 2.04 - 1.91 (m, 7H), 1.94 - 1.78 (m, 3H), 1.81 - 1.67 (m, 2H).

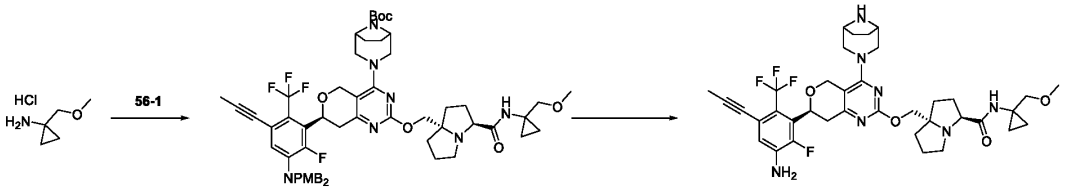
Example 160



With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **160-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-70%) to afford compound **160**. MS m/z = 726.6 $[M+H]^+$. ^1H NMR (400 MHz,

CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.11 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.11 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.75 - 3.64 (m, 2H), 3.57 - 3.49 (m, 3H), 3.44 - 3.38 (m, 1H), 3.26 - 3.17 (m, 1H), 3.07 - 3.01 (m, 1H), 2.93 - 2.82 (m, 2H), 2.78 - 2.71 (m, 1H), 2.14 - 2.07 (m, 2H), 2.05 - 1.95 (m, 5H), 1.94 - 1.80 (m, 8H), 1.79 - 1.68 (m, 4H), 1.66 - 1.61 (m, 1H), 1.41 - 1.31 (m, 2H), 1.30 - 1.20 (m, 3H).

Example 161



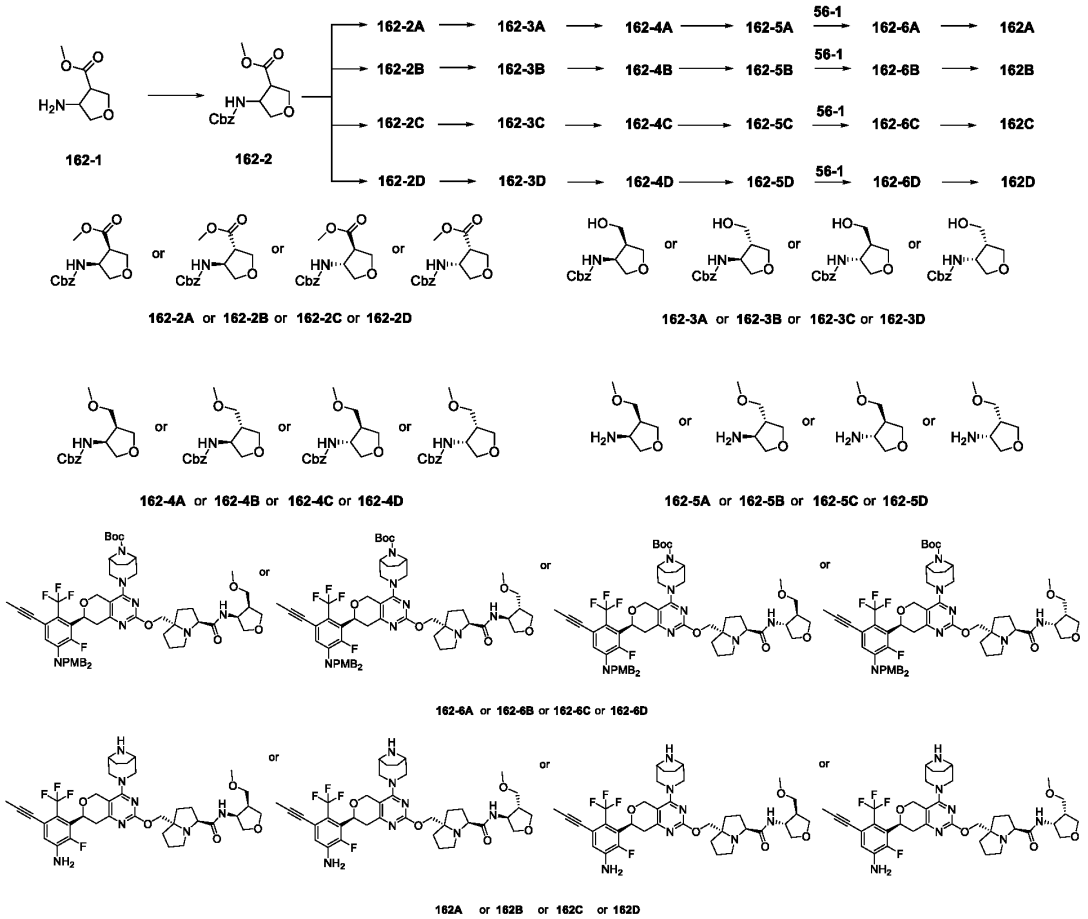
Step 1

To a stirred solution of compound **56-1** (50 mg, 50.76 μmol) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (32.80 mg, 253.78 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (28.95 mg, 76.14 μmol) and compound **161-1** (13.97 mg, 101.51 μmol). The mixture was stirred at 25 °C for 1 hour. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 20:1) to afford compound **161-2**. MS m/z = 1068.7 $[M+H]^+$.

Step 2

The mixture of compound **161-2** (45 mg, 42.12 μmol) in TFA (1 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 5%-50%) to afford compound **161**. MS m/z = 728.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.18 - 4.11 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.72 - 3.67 (m, 1H), 3.57 - 3.53 (m, 2H), 3.52 - 3.49 (m, 1H), 3.48 - 3.36 (m, 3H), 3.34 (s, 3H), 3.27 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.78 - 2.70 (m, 1H), 2.15 - 2.05 (m, 2H), 2.04 - 1.99 (m, 4H), 1.99 - 1.87 (m, 5H), 1.87 - 1.81 (m, 2H), 1.77 - 1.66 (m, 2H), 0.84 - 0.72 (m, 4H).

Example 162



Step 1

To a solution of compound **162-1** (1.2 g, 8.27 mmol) in THF (30 mL) and water (30 mL) was added Na_2CO_3 (2.63 g, 24.80 mmol) and CbzCl (2.12 g, 12.40 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was quenched with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 8:1) to afford compound **162-2**, MS m/z = 280.0 $[M+H]^+$. Chiral Separation of Compound **162-2** by SFC (Column: DAICEL CHIRALPAK®AD-10, 25*250 mm 10 μm; Mobile phase: A: Supercritical CO_2, B: MeOH (0.05% - NH_3); B%, 20%) to obtain compounds **162-2A**, **162-2B**, **162-2C** and **162-2D**. SFC Analysis methods (DAICEL CHIRALPAK®AD-3 (100*3 mm, 3 μm); Mobile phase: A: Supercritical CO_2; B: (MeOH(0.05% - DEA), 5% -40%, 4 min). compound **162-2A**, Rt=2.317 mins, ee: 97.96%, MS m/z = 280.0 $[M+H]^+$; compound **162-2B**, Rt=2.817 mins, ee : 100%, MS m/z = 280.0 $[M+H]^+$; compound **162-2C**, Rt=2.951 mins, ee : 99.12%, MS m/z = 280.0 $[M+H]^+$; compound **162-2D**, Rt=3.332 mins, ee : 100%, MS m/z = 280.0 $[M+H]^+$.

Step 2

To a solution of compound **162-2A** (190 mg, 680.30 μmol) in dry THF (2 mL) was added lithium aluminum hydride (77.46 mg, 2.04 mmol, 2.5 M in THF) at -60 °C. The mxiture was stirred at -60 °C for 2 hours. The mixture was diluted with DCM (10 mL), quenched with water (0.1 mL) and 15% aq. NaOH (0.1 mL) and stirred for 10 minutes. The reaction mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 40:1) to afford compound **162-3A**. MS m/z = 252.2 $[M+H]^+$.

With reference to step 2, compound **162-2A** was replaced with compound **162-2B** as the raw material to obtain compound **162-3B**. MS m/z = 252.2 $[M+H]^+$.

With reference to step 2, compound **162-2A** was replaced with compound **162-2C** as the raw material to obtain compound **162-3C**. MS m/z = 252.2 $[M+H]^+$.

With reference to step 2, compound **162-2A** was replaced with compound **162-2D** as the raw material to obtain compound **162-3D**. MS m/z = 252.2 $[M+H]^+$.

Step 3

To a solution of compound **162-3A** (115 mg, 457.66 μmol) in DCM (3 mL) was added 4Å molecular sieves (780.15 mg), trimethyloxonium tetrafluoroborate (135.38 mg, 915.32 μmol) and proton sponge (245.20 mg, 1.14 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 1:1) to afford compound **162-4A**. MS m/z = 266.2 $[M+H]^+$.

With reference to step 3, compound **162-3A** was replaced with compound **162-3B** as the raw material to obtain compound **162-4B**. MS m/z = 266.2 $[M+H]^+$.

With reference to step 3, compound **162-3A** was replaced with compound **162-3C** as the raw material to obtain compound **162-4C**. MS m/z = 266.2 $[M+H]^+$.

With reference to step 3, compound **162-3A** was replaced with compound **162-3D** as the raw material to obtain compound **162-4D**. MS m/z = 266.2 $[M+H]^+$.

Step 4

To a solution of compound **162-4A** (65 mg, 245.00 μmol) in MeOH (10 mL) was added Pd/C (26.07 mg, 10% purtiy). The mixture was stirred at 20 °C for 16 hours under H_2 atmosphere(15 psi). The mixture was filtered and concentrated to afford compound **162-5**A. MS m/z = 132.1 $[M+H]^+$.

With reference to step 4, compound **162-4A** was replaced with compound **162-4B** as the raw material to obtain compound **162-5B**. MS m/z = 132.1 $[M+H]^+$.

With reference to step 4, compound **162-4A** was replaced with compound **162-4C** as the raw material to obtain compound **162-5C**. MS m/z = 132.1 $[M+H]^+$.

With reference to step 4, compound **162-4A** was replaced with compound **162-4D** as the raw material to obtain compound **162-5D**. MS m/z = 132.1 $[M+H]^+$.

Step 5

To a solution of compound **162-5A** (11.98 mg, 91.36 μmol) in DCM (1.0 mL) was added O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (39.37 mg, 103.55 μmol), N,N-diisopropylethylamine (23.62 mg, 182.73 μmol) and compound **56-1** (60 mg, 60.91 μmol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The reaction was concentrated in vacuum to remove the solvent. The residue was purified by flash chromatography (PE: EtOAc = 0:1) to afford compound **162-6A**. MS m/z = 1098.7 $[M+H]^+$.

With reference to step 5, compound **162-5A** was replaced with compound **162-5B** as the raw material to obtain compound **162-6B**. MS m/z = 1098.7 $[M+H]^+$.

With reference to step 5, compound **162-5A** was replaced with compound **162-5C** as the raw material to obtain compound **162-6C**. MS m/z = 1098.7 $[M+H]^+$.

With reference to step 5, compound **162-5A** was replaced with compound **162-5D** as the raw material to obtain compound **162-6D**. MS m/z = 1098.7 $[M+H]^+$.

Step 6

To a solution of compound **162-6A** (30 mg, 27.37 μmol) in DCM (1 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated in vacuum. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford Compound **162A**. MS m/z = 758.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.59 - 4.53 (m, 1H), 4.18 - 4.13 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.99 - 3.92 (m, 2H), 3.81 - 3.77 (m, 1H), 3.72 - 3.63 (m, 2H), 3.57 - 3.47 (m, 4H), 3.46 - 3.32 (m, 3H), 3.29 - 3.11 (m, 3H), 3.04 (d, J = 12.0 Hz, 1H), 2.95 - 2.81 (m, 2H), 2.75 - 2.64 (m, 2H), 2.15 - 2.03 (m, 3H), 2.02 (s, 3H), 1.97 - 1.88 (m, 4H), 1.86 - 1.80 (m, 2H), 1.77 - 1.64 (m, 3H).

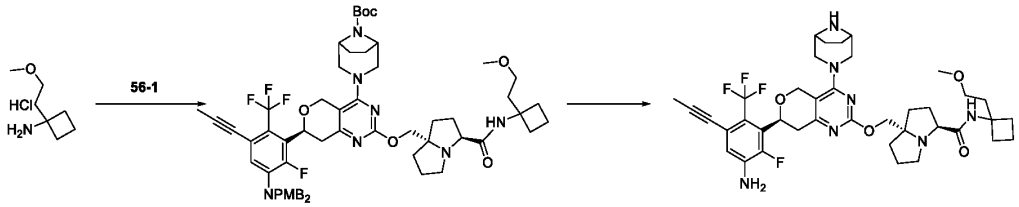
To a solution of compound **162-6B** (65 mg, 29.59 μmol) in DCM (1 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated in vacuum. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford Compound **162B**. MS m/z = 758.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.14 (dd, J = 8.0, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.21 - 4.10 (m, 3H), 4.08 - 3.90 (m,

3H), 3.81 - 3.72 (m, 1H), 3.62 - 3.50 (m, 5H), 3.49 - 3.37 (m, 3H), 3.34 (s, 3H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.94 - 2.79 (m, 2H), 2.78 - 2.66 (m, 1H), 2.46 - 2.34 (m, 1H), 2.15 - 2.06 (m, 2H), 2.05 - 2.00 (m, 4H), 2.00 - 1.86 (m, 5H), 1.85 - 1.79 (m, 2H), 1.77 - 1.66 (m, 2H).

To a solution of compound **162-6C** (65 mg, 29.59 μmol) in DCM (1 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated in vacuum. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford Compound **162C**. MS m/z = 758.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.16 - 5.12 (m, 1H), 4.81 - 4.78 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.23 - 4.10 (m, 3H), 4.07 - 3.93 (m, 3H), 3.79 - 3.72 (m, 1H), 3.61 - 3.53 (m, 4H), 3.51 - 3.37 (m, 4H), 3.34 - 3.32 (m, 3H), 3.21 (dd, J = 16.0, 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.95 - 2.88 (m, 1H), 2.88 - 2.72 (m, 2H), 2.47 - 2.35 (m, 1H), 2.14 - 2.06 (m, 2H), 2.04 - 2.00 (m, 4H), 1.99 - 1.87 (m, 5H), 1.86 - 1.80 (m, 2H),1.77 - 1.66 (m, 2H).

To a solution of compound **162-6D** (65 mg, 29.59 μmol) in DCM (1 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated in vacuum. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford Compound **162D**. MS m/z = 758.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.20 - 5.07 (m, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.57 - 4.52 (m, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, J = 8.0 Hz, 1H), 4.01 - 3.91 (m, 2H), 3.80 - 3.77 (m, 1H), 3.70 (t, J = 8.0 Hz, 1H), 3.64 (dd, J = 8.0, 4.0 Hz, 1H), 3.58 - 3.48 (m, 4H), 3.47 - 3.38 (m, 2H), 3.31 (s, 3H), 3.21 (dd, J = 20.0, 12.0 Hz, 1H), 3.04 (d, J = 16.0 Hz, 1H), 2.98 - 2.93 (m, 1H), 2.86 - 2.76 (m, 2H), 2.71 - 2.63 (m, 1H), 2.15 - 2.07 (m, 2H), 2.05 - 1.98 (m, 5H), 1.97 - 1.87 (m, 4H), 1.86 - 1.80 (s, 2H), 1.79 - 1.68 (m, 2H).

Example 163



163-1 163-2 163

Step 1

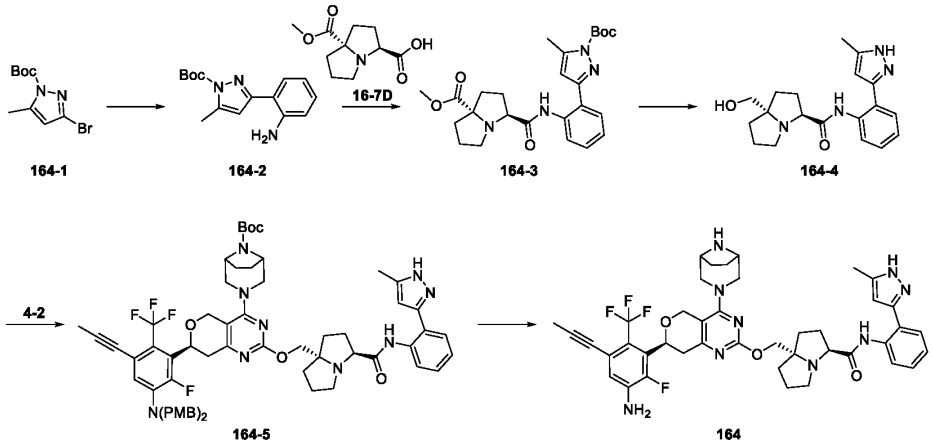
To a stirred solution of compound **56-1** (50 mg, 50.76 μmol) in DCM (2.0 mL) was added N,N-diisopropylethylamine (19.68 mg, 152.27 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-

tetraMethyluroniuM hexafluorophosphate (38.60 mg, 101.52 μmol) and compound **163-1** (19.68 mg, 152.28 μmol). The resulting mixture was stirred at 25 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **163-2**. MS m/z = 1096.8 $[M+H]^+$.

Step 2

To a solution of compound **163-2** (30 mg, 27.37 μmol) in DCM (1 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction was concentrated in vacuum. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford Compound **163.** MS m/z = 756.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.92 (d, J = 8.0 Hz, 1H), 5.21 - 5.13 (m, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.23 - 4.13 (m, 2H), 4.07 (d, J = 12.0 Hz, 1H), 3.78 - 3.71 (m, 1H), 3.60 - 3.51 (m, 3H), 3.50 - 3.41 (m, 3H), 3.30 (s, 3H), 3.28 - 3.19 (m, 1H), 3.06 (d, J = 12.0 Hz, 1H), 3.03 - 2.93 (m, 1H), 2.92 - 2.77 (m, 2H), 2.30 - 2.24 (m, 2H), 2.20 - 2.06 (m, 6H), 2.01 (s, 3H), 2.01 - 1.79 (m, 10H), 1.76 - 1.67 (m, 2H).

Example 164



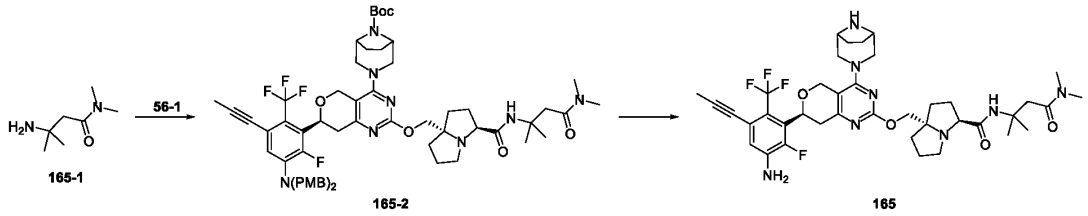
Step 1

A mixture of **164-1** (300 mg, 1.15 mmol), 2-aminophenylboronic acid (188.80 mg, 1.38 mmol), Pd (dppf) Cl_2 (168.13 mg, 229.78 μmol) and K_2CO_3 (476.36 mg, 3.45 mmol) in dioxane (8 mL) andwater (2 mL) was stirred at 90 ° for 4 hours under N_2 atomosphere. The mixture was quenched with water (2 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 10:1) to afford compound **164-2**. MS m/z =274.2 $[M+H]^+$.

Step 2

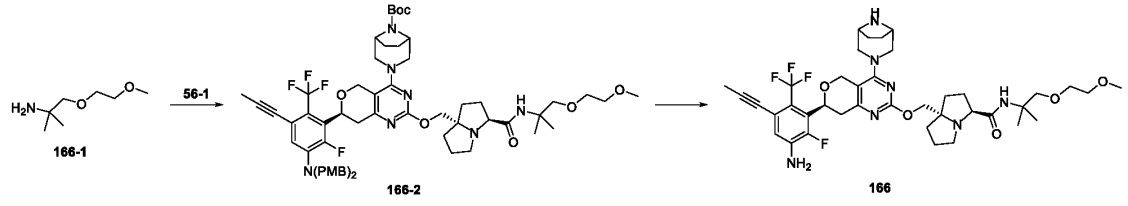
With reference to steps 7~10 of **Example 16**, N-ethyl-4-methoxybenzylamine was replaced with compound **164-2** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-80%) to afford compound **164**. MS m/z = 800.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.98 (s, 1H), 11.80 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.13 - 7.09 (m, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 6.02 (s, 2H), 5.04 (dd, J = 8.0, 4.0 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 12.0 Hz, 2H), 3.79 (t, J = 12.0 Hz, 1H), 3.43 - 3.38 (m, 4H), 3.25 (s, 1H), 3.09 - 3.02 (m, 1H), 2.90 - 2.78 (m, 3H), 2.64 - 2.60 (m, 1H), 2.30 (s, 3H), 2.16 - 2.07 (m, 2H), 2.03 (s, 3H), 1.97 - 1.93 (m, 1H), 1.89 - 1.77 (m, 5H), 1.66 - 1.54 (m, 4H).

Example 165



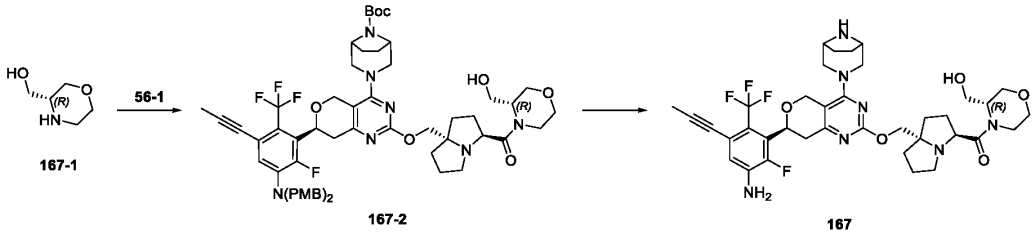
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **165-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **165**. MS m/z = 771.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.18 - 4.13 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.57 - 3.52 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 16.0 Hz, 8.0 Hz, 1H), 3.10 (s, 3H), 3.05 (d, J = 12.0 Hz, 1H), 3.01 - 2.95 (m, 1H), 2.93 - 2.90 (m, 4H), 2.87 - 2.79 (m, 2H), 2.77 - 2.70 (m, 1H), 2.15 - 2.04 (m, 3H), 2.02 (s, 3H), 1.95 - 1.83 (m, 7H), 1.75 - 1.70 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H).

Example 166



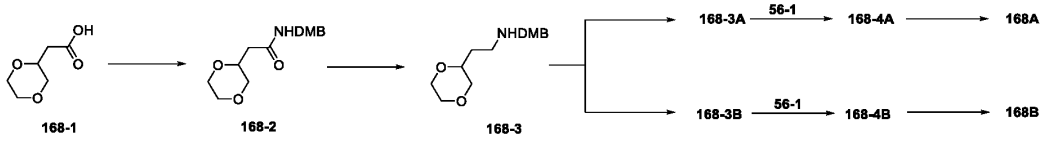
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **166-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% FA); Gradient: (ACN): 20%-65%) to afford compound **166** as FA salt. MS m/z = 774.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (s, 1.32H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.81 (s, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.30 - 4.15 (m, 3H), 3.99 - 3.90 (m, 3H), 3.71 - 3.67 (m, 1H), 3.62 - 3.52 (m, 6H), 3.48 - 3.46 (m, 1H), 3.34 (s, 3H), 3.27 - 3.17 (m, 3H), 2.98 - 2.87 (m, 2H), 2.22 - 2.13 (m, 3H), 2.05 - 1.81 (m, 12H), 1.34 (s, 3H), 1.33 (s, 3H).

Example 167



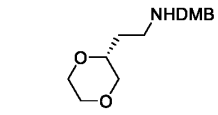
With reference to steps 2~3 of **Example 56**, (S)-3,3-difluorocyclopentanamine hydrochloride was replaced with compound **167-1** as the raw material to obtain crude product. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm; ACN-H_2O (0.1% NH_3); Gradient: (ACN): 35%-75%) to afford compound **167**. MS m/z = 744.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.91 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.67 - 4.62 (m, 1H), 4.48 - 4.30 (m, 2H), 4.11 - 4.01 (m, 2H), 3.97 (s, 1H), 3.94 - 3.86 (m, 1H), 3.85 - 3.77 (m, 1H), 3.73 - 3.52 (m, 5H), 3.49 - 3.35 (m, 4H), 3.24 - 3.14 (m, 2H), 3.08 (d, *J* = 12.0 Hz, 1H), 2.88 - 2.83 (m, 2H), 2.61 - 2.49 (m, 1H), 2.20 - 2.13 (m, 1H), 2.08 - 2.04 (m, 1H), 2.02 (s, 3H), 1.96 - 1.71 (m, 8H), 1.63 - 1.52 (m, 2H).

Example 168

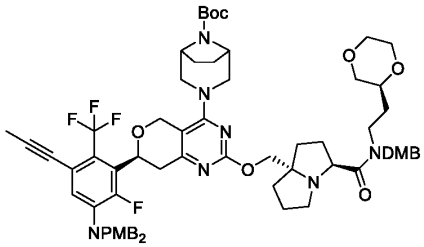




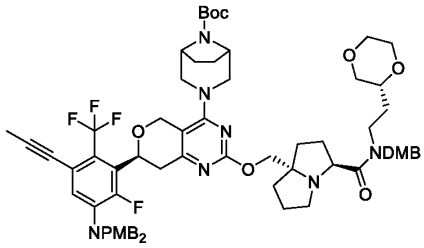
168-3A or 168-3B



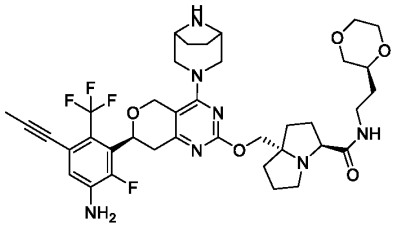
168-3A or 168-3B



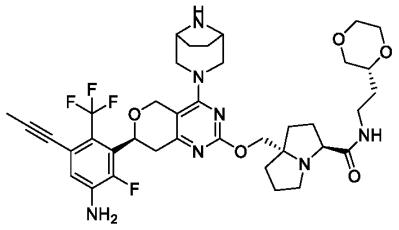
168-4A or 168-4B



168-4A or 168-4B



168A or 168B



168A or 168B

Step 1

To a solution of compound **168-1** (200 mg, 1.37 mmol) in N,N-dimethylformamide (4 mL) was added O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (5.10 g, 50.41 mmol), N,N-diisopropylethylamine (530.62 mg, 4.11 mmol) and 2,4-dimethoxybenzylamine (457.65 mg, 2.74 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hours. The mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 1:1) to afford compound **168-2**. MS m/z = 296.1 $[M+H]^+$.

Step 2

To a solution of compound **168-2** (450 mg, 1.52 mmol) in THF (10 mL) was added lithium aluminum hydride (2.5 M, 4.57 mmol, 1.83 mL) at 0 °C. The mixture was stirred at 60 °C for 12 hours. The mixture was quenched with water (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reversed phase to afford compound **168-3**. MS m/z = 281.95 $[M+H]^+$. Chiral Separation of Compound **168-3** by SFC (Column: Regis (S,S)Whelk-O1, 25*250 mm 10 μm; Mobile phase: A: hexane, B: EtOH; B%, 20%) to obtain compounds **168-3A**

and **168-3B**. SFC Analysis methods (chromatographic column: Regis (s,s) WHELK-01(4.6 mmI.D*150 mmL, 5 μm); Mobile phase: A: Supercritical CO_2; B: (IPA (0.05% - DEA), 5% -40%, 15 min). compound **168-3A**, Rt = 7.591 mins, ee: 99.38%, MS m/z = 281.99 $[M+H]^+$; compound **168-3B**, Rt=9.609 mins, ee : 92.14%, MS m/z = 281.96 $[M+H]^+$.

Step 3

To a solution of compound **168-3A** (70 mg, 248.80 μmol) in N,N-dimethylformamide (2 mL) was added **56-1** (269.60 mg, 273.68 μmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetraMethyluroniuM hexafluorophosphate (5.10 g, 50.41 mmol) and N,N-diisopropylethylamine (530.62 mg, 4.11 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hours. The mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 1:1) to afford compound **168-4A**. MS m/z = 1248.9 $[M+H]^+$.

With reference to step 3, compound **168-3A** was replaced with compound **168-3B** as the raw material to obtain compound **168-4B**. m/z = 1248.9 $[M+1]^+$.

Step 4

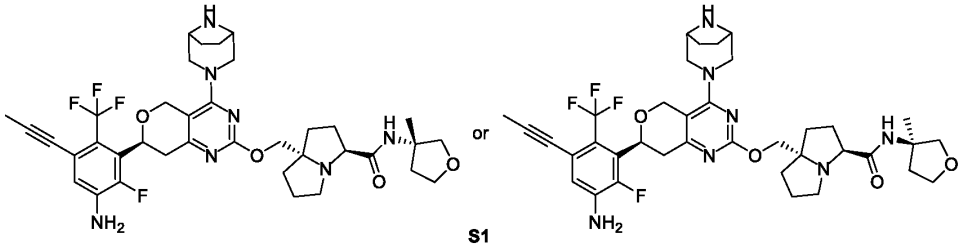
The mixture of compound **168-4A** (0.14 g, 138.32 μmol) in TFA (2 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **168A**. MS m/z = 758.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.77 - 3.64 (m, 5H), 3.61 - 3.49 (m, 5H), 3.45 - 3.39 (m, 1H), 3.37 - 3.33 (m, 1H), 3.30 - 3.16 (m, 3H), 3.04 (d, J = 12.0 Hz, 1H), 2.95 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.77 - 2.70 (m, 1H), 2.14 - 2.07 (m, 2H), 2.02 (s, 5H), 1.95 - 1.81 (m, 6H), 1.77 - 1.68 (m, 2H), 1.60 - 1.53 (m, 2H).

The mixture of compound **168-4B** (110 mg, 88.11 μmol) in TFA (1 mL) and DCM (3 mL) was stirred at 25 °C for 0.5 hours. The reaction was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **168B**. MS m/z = 758.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81-4.78 (m, 1H), 4.66 - 4.63(m, 1H), 4.18 - 4.13(m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.82 - 3.63 (m, 5H), 3.63 - 3.46 (m, 5H), 3.45 - 3.33 (m, 2H), 3.29 - 3.13 (m, 3H), 3.06 - 3.02 (m, 1H), 2.96-2.67 (m, 3H), 2.15 - 2.06 (m, 2H), 2.02 (s, 3H), 2.00 - 1.81 (m, 8H), 1.77 - 1.64 (m, 2H), 1.60-1.50 (m, 2H).

Example S1

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-3-methyltetrahydrofuran-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-3-methyltetrahydrofuran-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide

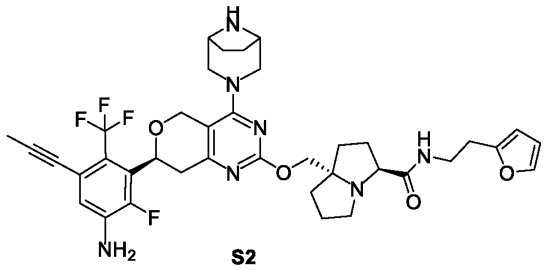


S1

Compound **S1** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **41-3A** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm 5mm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-80%) to afford Compound **S1**. LCMS: $[M+H]^+$ = 728.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.81 - 4.77 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.11 (m, 2H), 4.08 - 4.02 (m, 1H), 4.00 - 3.95 (m, 1H), 3.93 - 3.86 (m, 2H), 3.76 - 3.70 (m, 1H), 3.68 - 3.63 (m, 1H), 3.56 - 3.49 (m, 3H), 3.45 - 3.39 (m, 1H), 3.26 - 3.18 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.95 - 2.81 (m, 2H), 2.79 - 2.70 (m, 1H), 2.35 - 2.27 (m, 1H), 2.15 - 2.06 (m, 2H), 2.01 (s, 3H), 2.00 - 1.86 (m, 7H), 1.85 - 1.80 (m, 2H), 1.76 - 1.66 (m, 2H), 1.48 (s, 3H).

Example S2

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(furan-2-yl)ethyl)hexahydro-1H-pyrrolizine-3-carboxamide

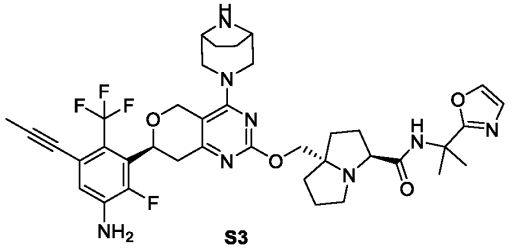


S2

Compound **S2** was prepared analogous to compound **155** (CN 2024/083328), replacing intermediate **155-1** with 2-furan-2-yl-ethylamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **S2**. LCMS: $[M+H]^+$ = 738.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.37 - 7.36 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.30 - 6.29 (m, 1H), 6.12 - 6.11 (m, 1H), 5.14 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.16 - 4.12 (m, 2H), 4.04 (d, J = 12.0 Hz, 1H), 3.72 (dd, J = 8.0, 4.0 Hz, 1H), 3.56 - 3.46 (m, 5H), 3.44 - 3.40 (m, 1H), 3.21 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.87 - 2.81 (m, 4H), 2.71 - 2.65 (m, 1H), 2.12 - 2.05 (m, 2H), 2.03 - 1.98 (m, 5H), 1.94 - 1.81 (m, 6H), 1.75 - 1.66 (m, 2H).

Example S3

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(oxazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



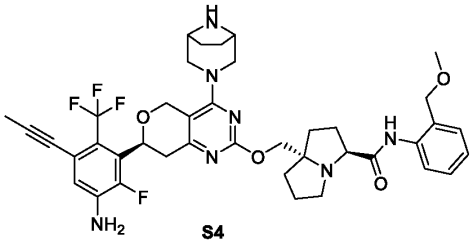
S3

Compound **S3** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-(oxazol-2-yl)propan-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-60%) to afford compound **S3**. LCMS: $[M+H]^+$ = 753.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.79 (d, J = 0.8 Hz, 1H), 7.08 (d, J = 0.8 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.18 - 4.14 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.79 (dd, J = 12.0, 4.0 Hz, 1H), 3.55 - 3.52 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 3.01 - 2.94 (m, 1H),

2.85 (dd, J = 20.0, 4.0 Hz, 1H), 2.74 - 2.68 (m, 1H), 2.15 - 1.98 (m, 6H), 1.94 - 1.83 (m, 7H), 1.72 - 1.64 (m, 8H).

Example S4

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(methoxymethyl)phenyl)hexahydro-1H-pyrrolizine-3-carboxamide

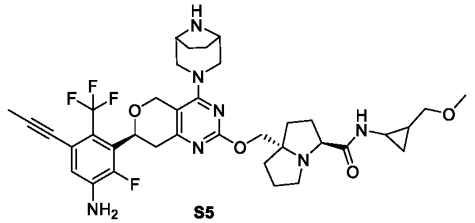


S4

Compound **S4** was prepared analogous to compound **16** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 2-(methoxymethyl)aniline. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **S4**. LCMS: $[M+H]^+$ = 764.5. ^1H NMR (400 MHz, CD_3OD) δppm 7.72 (d, J = 8.0 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.21 - 7.15 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.82 - 4.78 (m, 1H), 4.69 - 4.62 (m, 1H), 4.51 (s, 2H), 4.27 - 4.21 (m, 1H), 4.18 - 4.09 (m, 2H), 4.03 - 3.97 (m, 1H), 3.59 - 3.50 (m, 3H), 3.46 - 3.40 (m, 1H), 3.36 (s, 3H), 3.26 - 3.18 (m, 1H), 3.11 - 3.03 (m, 2H), 2.90 - 2.76 (m, 2H), 2.25 - 2.17 (m, 1H), 2.16 - 2.06 (m, 2H), 2.05 - 1.98 (m, 5H), 1.97 - 1.89 (m, 3H), 1.88 - 1.80 (m, 2H), 1.79 - 1.74 (m, 1H), 1.73 - 1.65 (m, 1H).

Example S5

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(methoxymethyl)cyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide



S5

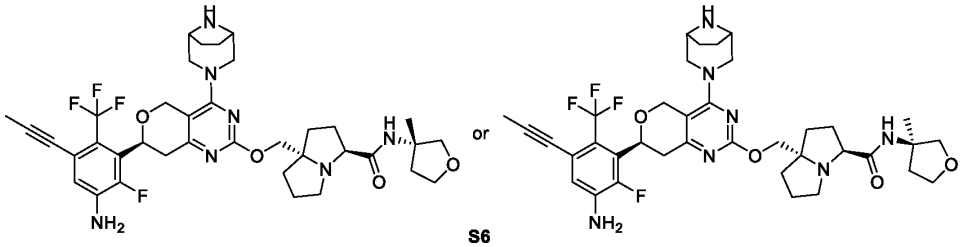
Compound **S5** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-

difluorocyclopentanamine hydrochloride with 2-(methoxymethyl)cyclopropan-1-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-65%) to afford compound **S5**. LCMS: $[M+H]^+$ = 728.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.24 - 5.08 (m, 1H), 4.80 - 4.76 (m, 1H), 4.67 - 4.63 (m, 1H), 4.24 - 4.07 (m, 3H), 3.78 - 3.67 (m, 1H), 3.65 - 3.44 (m, 4H), 3.43 - 3.39 (m, 1H), 3.26 - 3.01 (m, 5H), 3.00 - 2.91 (m, 2H), 2.89 - 2.80 (m, 1H), 2.76 - 2.64 (m, 1H), 2.62 - 2.47 (m, 1H), 2.31 - 2.10 (m, 2H), 2.09 - 1.97 (m, 5H), 1.93 - 1.78 (m, 6H), 1.75 - 1.62 (m, 2H), 1.15 - 0.79 (m, 2H), 0.73 - 0.43 (m, 1H).

Example S6

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-3-methyltetrahydrofuran-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-3-methyltetrahydrofuran-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide

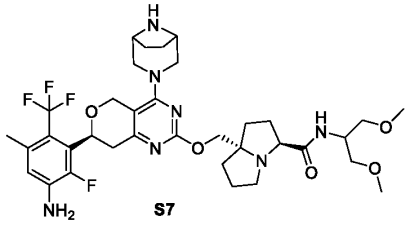


S6

Compound **S6** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **41-3B** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-80%) to afford Compound **S6**. LCMS: $[M+H]^+$ = 728.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.21 - 5.10 (m, 1H), 4.81 - 4.76 (m, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.21 - 4.10 (m, 2H), 4.09 - 3.98 (m, 2H), 3.95 - 3.85 (m, 2H), 3.78 - 3.71 (m, 1H), 3.66 - 3.61 (m, 1H), 3.57 - 3.48 (m, 3H), 3.43 - 3.38 (m, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, J = 16.0 Hz, 1H), 2.96 - 2.81 (m, 2H), 2.78 - 2.69 (m, 1H), 2.34 - 2.25 (m, 1H), 2.15 - 2.06 (m, 2H), 2.01 (s, 3H), 2.00 - 1.86 (m, 7H), 1.85 - 1.80 (m, 2H), 1.75 - 1.65 (m, 2H), 1.48 (s, 3H).

Example S7

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

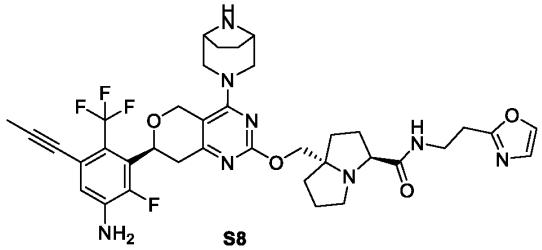


S7

Compound **S7** was prepared analogous to compound **82B** (CN 2024/083328), replacing intermediate **20-2D** (CN 2024/083328) with intermediate **6-3** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S7**. LCMS: $[M+H]^+$ = 722.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.72 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.13 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H),, 4.65 (d, *J* = 16.0 Hz, 1H), 4.29 - 4.12 (m, 3H), 4.06 (d, *J* = 12 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.60 - 3.50 (m, 3H), 3.49 - 3.40 (m, 5H), 3.34 (d, *J* = 4.0 Hz, 6H), 3.28 - 3.19 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.00 - 2.93 (m, 1H), 2.90 - 2.80 (m, 1H), 2.79 - 2.65 (m, 1H), 2.37 (q, *J* = 4.0 Hz, 3H), 2.18 - 2.07 (m, 2H), 2.04 - 1.80 (m, 8H), 1.77 - 1.64 (m, 2H).

Example S8

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(oxazol-2-yl)ethyl)hexahydro-1H-pyrrolizine-3-carboxamide



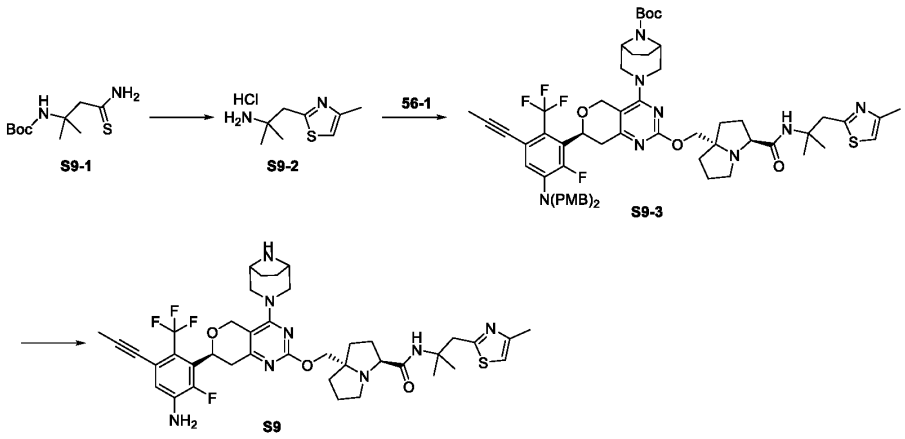
S8

Compound **S8** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-(oxazol-2-yl)ethan-1-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 25%-50%) to afford compound **S8**. LCMS: $[M+H]^+$ = 739.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 (d, *J* = 1.2 Hz, 1H), 7.08 (d, *J* = 1.2 Hz, 1H), 6.90 (d, *J* = 8.0 Hz,

1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.15 - 4.12 (m, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.73 - 3.69 (m, 1H), 3.66 - 3.58 (m, 2H), 3.54 - 3.50 (m, 3H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 - 3.00 (m, 3H), 2.89 - 2.78 (m, 2H), 2.70 - 2.63 (m, 1H), 2.13 - 2.04 (m, 2H), 2.03 - 1.96 (m, 5H), 1.93 - 1.79 (m, 6H), 1.75 - 1.63 (m, 2H).

Example S9

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-methyl-1-(4-methylthiazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S9-2

A solution of compound **S9-1** (200 mg, 860.80 μmol), bromoacetone (176.9 mg, 1.29 mmol) and calcium carbonate (86.2 mg, 860.80 μmol) in anhydrous EtOH (10 mL) was stirred for 24 hours at 80 °C. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was redissolved in DCM (3 mL), then HCl (2 mL, 4 M in dioxane) was added. The resulting mixture was stirred for 1 hour at 25 °C. The reaction was concentrated under reduced pressure to afford crude compound **S9-2**. LCMS: $[M+H]^+$ = 171.2.

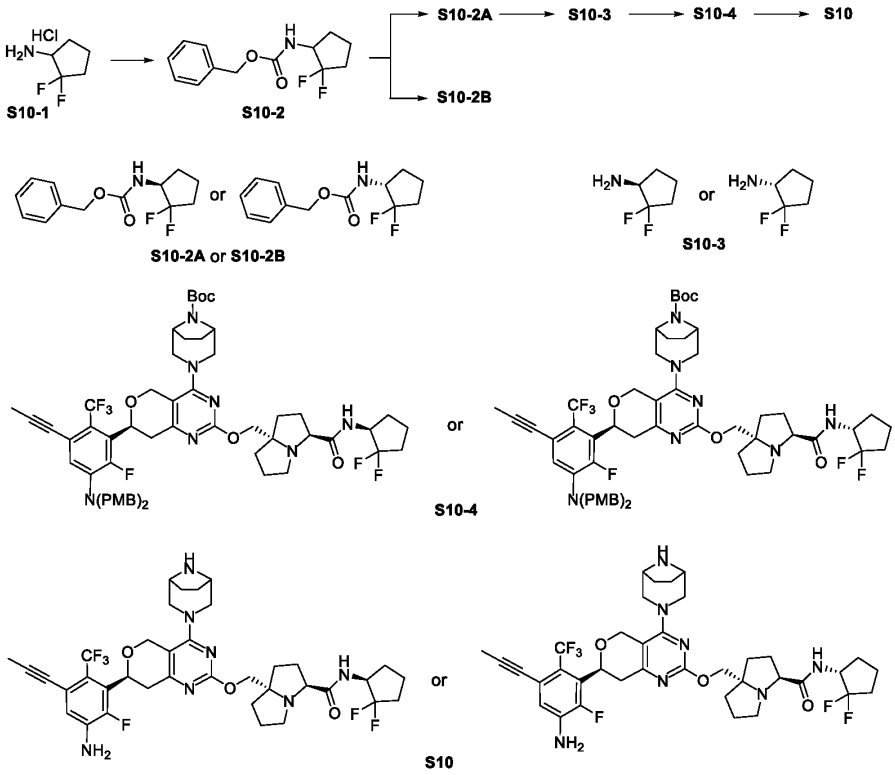
Step 2~3: S9

Compound **S9** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S9-2**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 45%-75%) to afford compound **S9**. LCMS: $[M+H]^+$ = 797.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.00 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.04 (d, *J* = 8.0 Hz, 1H), 3.76 - 3.71 (m,

2H), 3.54 - 3.51 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.26 - 3.17 (m, 2H), 3.05 (d, J = 12.0 Hz, 1H), 2.93 - 2.89 (m, 1H), 2.87 - 2.76 (m, 2H), 2.39 (s, 3H), 2.18 - 2.08 (m, 2H), 2.01 - 1.96 (m, 5H), 1.94 - 1.80 (m, 6H), 1.77 - 1.65 (m, 2H), 1.47 (s, 3H), 1.29 (s, 3H).

Example S10

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-2,2-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide or (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-2,2-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S10-2 and S10-2A & S10-2B

To a stirred solution of compound **S10-1** (800 mg, 5.08 mmol) in DCM (10 mL) was added K_2CO_3 (2.81 g, 20.31 mmol) and benzyl chloroformate (1.73 g, 10.15 mmol) at rt. The mixture was stirred at 25 °C for 4 hours. The reaction was diluted with water (10 mL), extracted wtih DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **S10-2**. LCMS: $[M+H]^+$ = 256.2.

The compound **S10-2** was separated by preparative SFC (System: Waters SFC 150, Column name: Regis®(S,S)Whelk-O 1, Column size: 4.6*150mm, 5 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +(0.05%) Diethylamine; Gradient: B% 5%-40% in 5 minutes; Wavelength: 214 nm/254nm, Flow Rate: 30 mL/ minute, Column temp: rt) to afford compound **S10-2A**, Rt = 2.133 minutes, >99.90% ee, LCMS: $[M+H]^+$ = 256.2; compound **S10-2B**, Rt = 2.406 minutes, >99.90% ee, LCMS: $[M+H]^+$ = 256.2.

Step 2: S10-3

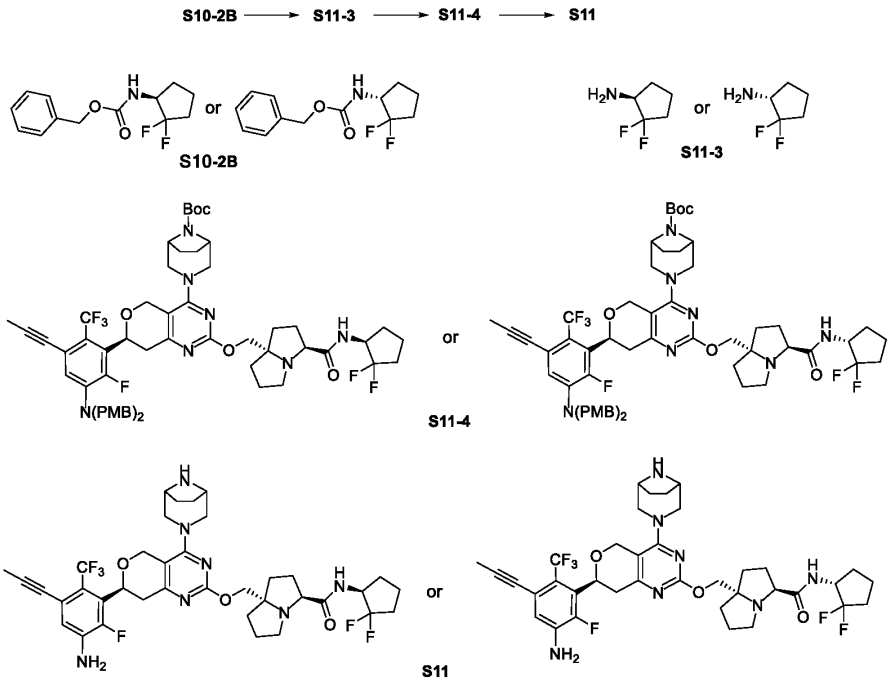
To a stirred solution of compound **S10-2A** (200 mg, 783.70 μmol) in methanol (2 mL) was added Pd/C (100 mg, 940.22 μmol) and the mixture was stirred at 25 °C for 4 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was washed with methanol (5 mL). To the combined filtrate was added HCl/dioxane (1 mL, 4.0 M). The mixture was stirred at rt for 3 hours. The mixture was concentrated under reduced pressure to afford compound **S10-3**. LCMS: $[M+H]^+$ = 122.1.

Step 3~4：S10

Compound **S10** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S10-3**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_4HCO_3); Gradient: (ACN): 50%-85%) to afford compound **S10**. LCMS: $[M+H]^+$ = 748.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.18 - 4.12 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.83 - 3.79 (m, 1H), 3.55 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.00 - 2.96 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.77 - 2.71 (m, 1H), 2.22 - 2.07 (m, 5H), 2.04 - 1.96 (m, 5H), 1.95 - 1.82 (m, 7H), 1.80 - 1.62 (m, 4H).

Example S11

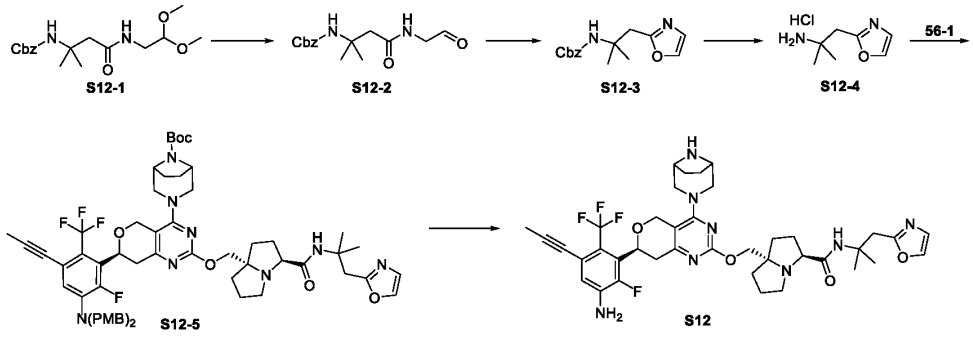
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-2,2-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide or (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-2,2-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



Compound **S11** was prepared analogous to compound **S10**, replacing intermediate **S10-2A** with intermediate **S10-2B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_4HCO_3); Gradient: (ACN): 50%-85%) to afford compound **S11**. LCMS: $[M+H]^+$ = 748.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.48 - 4.37 (m, 1H), 4.19 - 4.12 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.83 (dd, J = 8.0, 4.0 Hz, 1H), 3.54 - 3.51 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 20.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.76 - 2.69 (m, 1H), 2.23 - 2.06 (m, 5H), 2.05 - 1.99 (m, 5H), 1.97 - 1.81 (m, 7H), 1.79 - 1.61 (m, 4H).

Example S12

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-methyl-1-(oxazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S12-2

To a stirred solution of compound **S12-1** (4.5 g, 13.30 mmol) in THF (20 mL) was added 6 M HCl (10 mL), the mixture was stirred at 25 °C for 6 hours. The reaction was diluted with water (10 mL), adjust to pH = 8 with ammonium hydroxide (25~28%), then extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:3) to afford compound **S12-2**. LCMS: $[M+H]^+$ = 293.2.

Step 2: S12-3

To a stirred solution of PPh_3 (1.32 g，5.03 mmol), iodine (1.28 g，5.03 mmol) and triethylamine (1.02 g，10.06 mmol) in DCM (15 mL) was added the solution of compound **S12-2** (980 mg，3.35 mmol) in DCM (5 mL) at 25 °C. The reaction was stirred at 25 °C for 6 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 1:1) to afford compound **S12-3**. LCMS: $[M+H]^+$ = 275.1.

Step 3: S12-4

To a stirred solution of compound **S12-3** (270 mg，984.27 μmol) in methanol (5 mL) was added Pd/C (209.49 mg，196.85 μmol，10%) and the mixture was stirred at 25 °C for 8 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filter was washed with methanol (20 mL). To the combined filtrate was added HCl (1 mL, 4.0 M in dioxane). The mixture was stirred at 25 °C for 3 hours. The mixture was concentrated under reduced pressure to afford compound **S12-4**. LCMS: $[M+H]^+$ = 141.2.

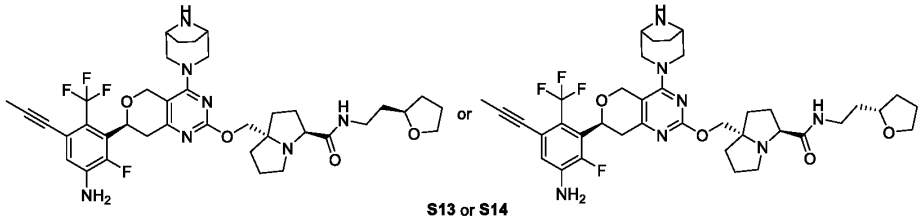
Steps 4~5：S12

Compound **S12** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S12-4**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, CAN-H_2O (0.1%NH_4HCO_3); Gradient: (CAN): 40%-70%) to afford compound **S12**. LCMS: $[M+H]^+$ = 767.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 (d, *J* = 0.8 Hz, 1H), 7.09 (d, *J* = 0.8 Hz, 1H), 6.90 (d, *J* =

8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.73 - 3.69 (m, 1H), 3.55 - 3.51 (m, 3H), 3.48 - 3.41 (m, 2H), 3.24 - 3.18 (m, 2H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.77 (m, 3H), 2.14 - 2.07 (m, 2H), 2.05 - 1.96 (m, 5H), 1.94 - 1.81 (m, 6H), 1.77 - 1.70 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H).

Example S13 and S14

(3S,8S)-8-[[(7S)-7-[3-amino-2-fluoro-5-prop-1-ynyl-6-(trifluoromethyl)phenyl]-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl]oxymethyl]-N-[2-[(2R*)-tetrahydrofuran-2-yl]ethyl]-1,2,3,5,6,7-hexahydropyrrolizine-3-carboxamide or (3S,8S)-8-[[(7S)-7-[3-amino-2-fluoro-5-prop-1-ynyl-6-(trifluoromethyl)phenyl]-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl]oxymethyl]-N-[2-[(2S*)-tetrahydrofuran-2-yl]ethyl]-1,2,3,5,6,7-hexahydropyrrolizine-3-carboxamide



S13 or S14

Compound **S13** and **S14** were prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride with 2-(tetrahydrofuran-2-yl)ethylamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, CAN-H_2O (0.1% NH_3); Gradient: (CAN): 60%-80%) to afford a mixture of compound **S13** and **S14**. LCMS: $[M+H]^+$ = 742.5. The mixture was separated by NP-HPLC (System: YMC, Column name: DAICEL CHIRALPAK®IC-10, 25*250 mm, 10 μm, Mobile Phase A: EtOH, ,Wavelength: 214 nm/254nm, Flow Rate: 30mL/min, Column temp: RT) to afford compound **S13** and **S14.** Chiral SFC analysis (chromatographic column: DAICEL CHIRALPAK®IC-H (150*4.6 mm, 5 μm); Mobile phase: EtOH+ (0.05%) DEA; CAN+ (0.05%) DEA, compound **S13,** Rt = 9.012 minutes, ee value 100%. Compound **S14,** Rt = 12.361 minutes, ee value 100%.

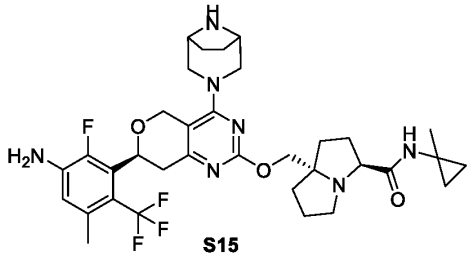
Compound **S13**: LCMS: $[M+H]^+$ = 742.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.81- 4.75 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.22 - 4.11 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.92 - 3.81 (m, 2H), 3.79 - 3.67 (m, 2H), 3.64 - 3.51 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.29 - 3.17 (m, 2H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.81 (m, 2H), 2.80 - 2.71 (m, 1H), 2.20 - 2.05 (m, 3H), 2.02 - 2.01 (m, 4H), 2.00 - 1.79 (m, 9H), 1.78 - 1.66 (m, 4H), 1.56 - 1.46 (m, 1H).

Compound **S14:** LCMS: $[M+H]^+$ = 742.6. ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 8.0 Hz,

1H), 5.19 - 5.10 (m, 1H), 4.81 - 4.76 (m, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.23 - 4.09 (m, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.94 - 3.80 (m, 2H), 3.78 - 3.65 (m, 2H), 3.60 - 3.49 (m, 3H), 3.42 (d, J = 8.0 Hz, 1H), 3.37 - 3.33 (m, 1H), 3.29 - 3.16 (m, 2H), 3.04 (d, J = 12.0 Hz, 1H), 2.96 - 2.79 (m, 2H), 2.78 - 2.68 (m, 1H), 2.16 - 2.08 (m, 2H), 2.07 - 1.97 (m, 6H), 1.96 - 1.78 (m, 8H), 1.77 - 1.64 (m, 4H), 1.57 - 1.46 (m, 1H).

Example S15

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-methylcyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide

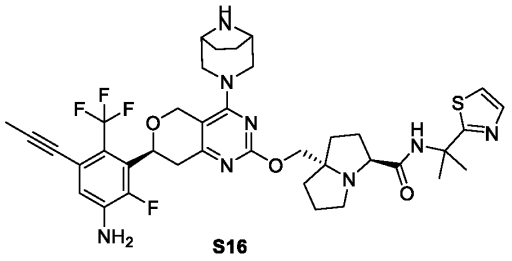


S15

Compound **S15** was prepared analogous to compound **82B** (CN 2024/083328), replacing intermediate **20-2D** (CN 2024/083328) with intermediate **2-2** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-60%) to afford compound **S15**. LCMS: $[M+H]^+$ = 674.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.69 (d, J = 8.0 Hz, 1H), 5.25 - 5.10 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.04 (d, J = 12.0 Hz, 1H), 3.72 - 3.54 (m, 4H), 3.47 - 3.39 (m, 1H), 3.27 - 3.19 (m, 1H), 3.07 (d, J = 16.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.81 - 2.72 (m, 1H), 2.36 (q, J = 4.0 Hz, 3H), 2.15 - 2.01 (m, 3H), 2.00 - 1.81 (m, 7H), 1.79 - 1.69 (m, 2H), 1.36 (s, 3H), 0.78 - 0.59 (m, 4H).

Example S16

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(thiazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

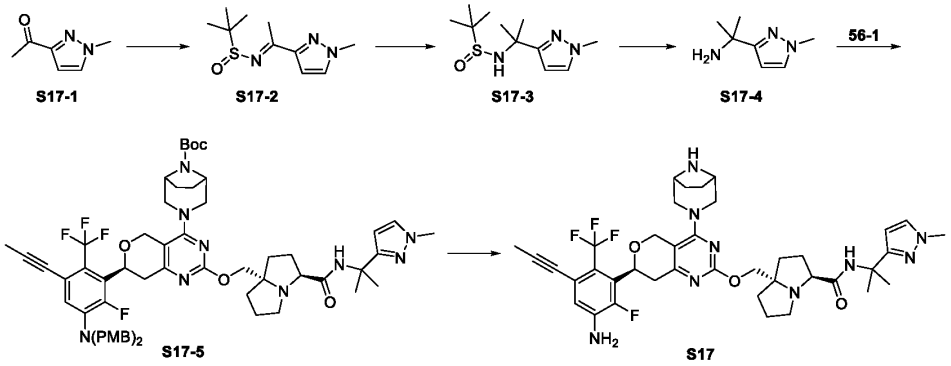


S16

Compound **S16** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-(thiazol-2-yl)propan-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S16**. LCMS: $[M+H]^+$ = 769.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.64 (d, *J* = 4.0 Hz, 1H), 7.45 (d, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.84 - 3.80 (m, 1H), 3.54 (d, *J* = 12.0 Hz, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.24 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.02 - 2.97 (m, 1H), 2.85 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.13 - 1.96 (m, 7H), 1.94 - 1.82 (m, 6H), 1.79 (s, 3H), 1.74 - 1.65 (m, 5H).

Example S17

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(1-methyl-1H-pyrazol-3-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



S17-1 S17-2 S17-3 S17-4 S17-5 S17

Step 1: S17-2

To a stirred solution of compound **S17-1** (1.7 g, 13.69 mmol) in dry THF (20 mL) was added tert-butanesulfinamide (1.99 g, 16.43 mmol) and titanium isopropoxide (11.68 g, 41.08 mmol) at 25 °C. The mixture was stirred at 70 °C for 16 hours. The reaction was concentrated under reduced

pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **S17-2**. LCMS: $[M+H]^+$ = 228.2.

Step 2: S17-3

To a stirred solution of compound **S17-2** (100 mg, 439.90 μmol) in dry THF (0.5 mL) was added methylmagnesium bromide (8.0 mL, 24.00 mmol, 3 M in THF) at 0 °C. The reaction was stirred at 25 °C for 16 hours. The reaction was quenched with saturated NH_4Cl solution (20 mL), extracted wtih EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse C18 chromatography (ACN-H_2O (0.1%NH_4HCO_3); Gradient: (ACN): 0%-30%) to afford compound **S17-3**. LCMS: $[M+H]^+$ = 244.2.

Step 3: S17-4

To a stirred solution of compound **S17-3** (50 mg, 205.45 μmol) in DCM (1 mL) was added concentrated HCl (0.3 mL, 37% in H_2O). The mixture was stirred at 25 °C for 1 hour. The mixture was concentrated under reduced pressure to afford compound **S17-4**. LCMS: $[M+H]^+$ = 140.1.

Steps 4~5：S17

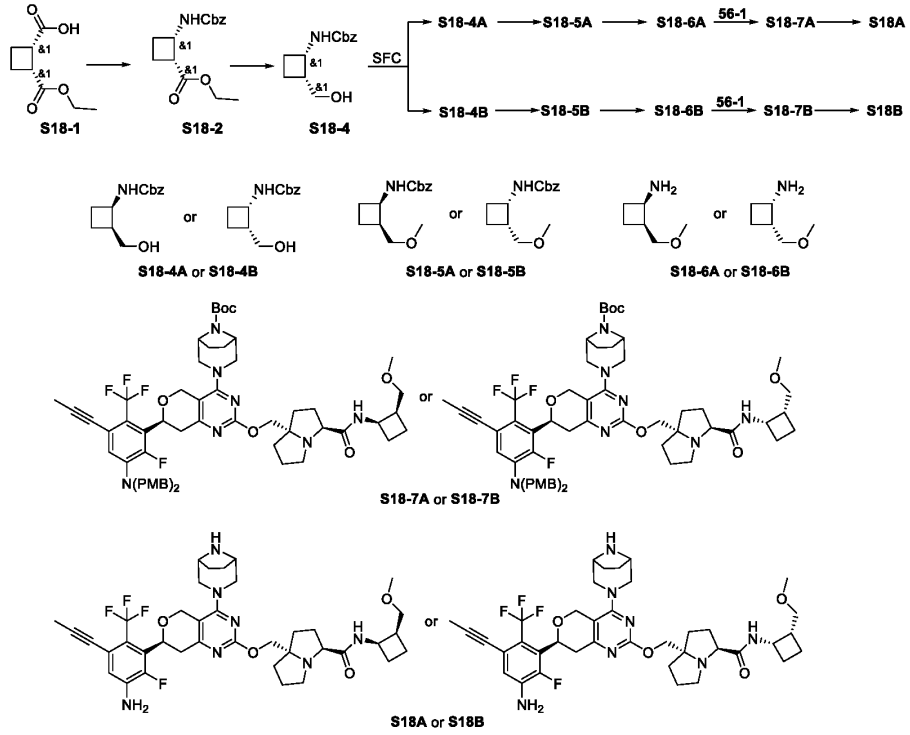
Compound **S17** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S17-4**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 35%-60%) to afford compound **S17**. LCMS: $[M+H]^+$ = 766.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.43 (d, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.18 (d, *J* = 4.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.83 (s, 3H), 3.80 - 3.76 (m, 1H), 3.56 - 3.52 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 16.0 Hz, 1H), 2.98 - 2.94 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.79 - 2.71 (m, 1H), 2.13 - 2.03 (m, 3H), 2.02 (s, 3H), 1.94 - 1.81 (m, 7H), 1.73 - 1.60 (m, 8H).

Example S18A and S18B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1R,2S)-2-(methoxymethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1S,2R)-2-(methoxymethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-

carboxamide



Step 1: S18-2

To a solution of compound **S18-1** (6.20 g, 36.01 mmol) in toluene (80 mL) was added TEA (5.10 g, 50.41 mmol) and DPPA (12.88 g, 46.81 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 3 hours under N_2 atmosphere. Benzyl alcohol was added above mixture, and the resulting mixture was stirred at 80 °C for 16 hours. After completion of reaction, the reaction mixture was concentrated in vacuum. The residue was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S18-2**. LCMS: $[M+H]^+$ = 278.1.

Step 2: S18-4 and S18-4A & S18-4B

To a solution of compound **S18-2** (2.0 g, 7.21 mmol) in MeOH (30 mL) was added MeONa (259.73 mg, 1.44 mol 30% purity in MeOH) and $NaBH_4$ (818.54 mg, 21.64 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was quenched with sat. NH_4Cl (60 mL) and extracted with DCM (3 x 30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 1:1) to afford compound **S18-4**. LCMS: $[M+H]^+$ = 236.1. Chiral Separation of Compound **S18-4** by SFC (Column: DAICEL CHIRALPAK®IC-10, 25*250mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: [IPA+(0.05%) NH_3 • MeOH]; B%, 20%) to obtain compounds **S18-4A** and **S18-4B**. SFC Analysis methods (chromatographic column: DAICEL

CHIRALPAK®IC-3 (3.0*100mm, 3μm); Mobile phase: A: Supercritical CO_2; B: (IPA (0.05% -DEA), 5% -40%). compound **S18-4A** Rt=3.075 mins, ee: 100%, LCMS: $[M+H]^+ = 236.1$; compound **S18-4B** Rt=3.404 mins, ee :100%, LCMS: $[M+H]^+ = 236.1$

Step 3：S18-5A

To a solution of compound **S18-4A** (480 mg, 2.04 mmol) in THF (30 mL) was added dimethyl sulfate (257.33 mg, 2.04 mmol) and KOH (400.62 mg, 7.14 mmol) at 25 °C. The mixture was stirred at 25 °C for 5 hours. The mixture was filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 7:1) to afford compound **S18-5A**. LCMS: $[M+H]^+ = 250.1$.

Step 4：S18-6A

To a solution of compound **S18-5A** (170 mg, 0.69 mmol) in THF (5 mL) was added Pd/C (20 mg, 10% purtiy). The mixture was stirred at 25 °C for 1 hour under H_2 atmosphere. The mixture was filtered and concentrated to afford compound **S18-6A**. LCMS: $[M+H]^+ = 116.1$.

Steps 5~6：S18A

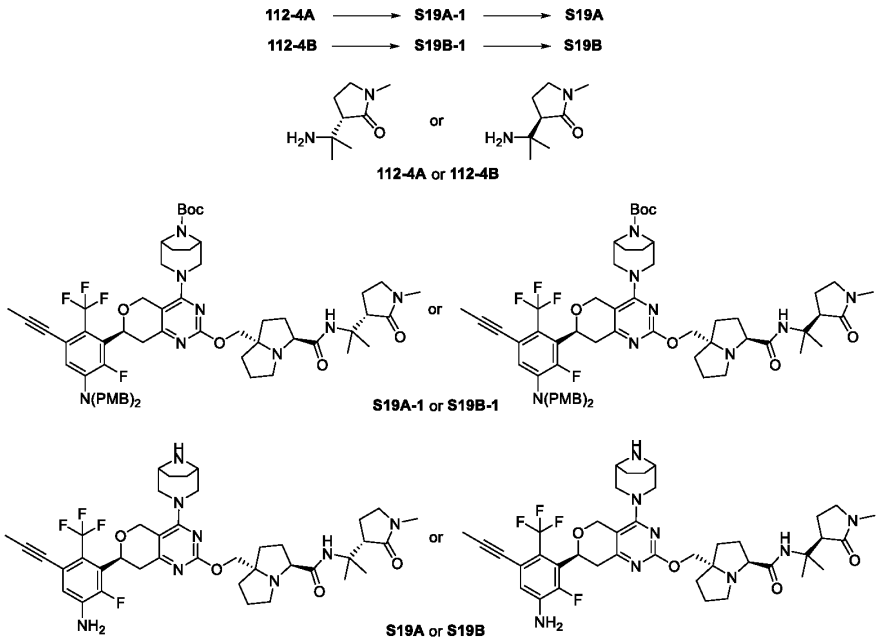
Compound **S18A** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S18-6A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-75%) to afford Compound **S18A**. MS m/z = 742.6 $[M+H]^+$。^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.10 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.53 - 4.44 (m, 1H), 4.19 - 4.10 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.60 - 3.48 (m, 5H), 3.45 - 3.39 (m, 1H), 3.34 (s, 3H), 3.25 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.94 (m, 1H), 2.88 - 2.81 (m, 1H), 2.80 - 2.72 (m, 2H), 2.33 - 2.25 (m, 1H), 2.14 - 1.89 (m, 13H), 1.85 - 1.64 (m, 5H).

Compound **S18B** was prepared analogous to compound **S18A**, replacing intermediate **S18-6A** with intermediate **S18-6B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-75%) to afford Compound **S18B**. MS m/z = 742.5 $[M+H]^+$。^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.10 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.53 - 4.44 (m, 1H), 4.19 - 4.12 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.61 - 3.51 (m, 4H), 3.49 - 3.41 (m, 2H), 3.33 (s, 3H), 3.25 - 3.17 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.82 (m, 2H), 2.79 - 2.68 (m, 2H), 2.33 - 2.25 (m, 1H), 2.14 - 1.89 (m, 13H), 1.85 - 1.62 (m, 5H).

Example S19A and S19B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-

((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-((S)-1-methyl-2-oxopyrrolidin-3-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide or
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-((S)-1-methyl-2-oxopyrrolidin-3-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



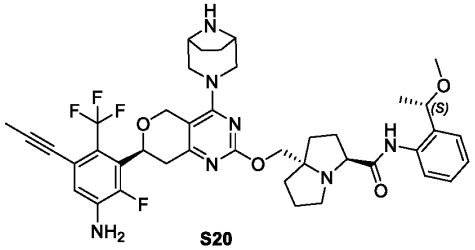
Compound **S19A** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **112-4A** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-55%) to afford compound **S19A**. LCMS: $[M+H]^+$ = 783.6。^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.81 - 4.76 (m, 1H), 4.70 - 4.62 (m, 1H), 4.26 - 4.02 (m, 3H), 3.81 - 3.72 (m, 1H), 3.69 - 3.40 (m, 5H), 3.39 - 3.33 (m, 2H), 3.28 - 3.17 (m, 2H), 3.12 - 2.98 (m, 2H), 2.88 - 2.77 (m, 4H), 2.22 - 2.04 (m, 4H), 2.02 (s, 3H), 2.00 - 1.79 (m, 8H), 1.78 - 1.67 (m, 2H), 1.45 (s, 3H), 1.35 (s, 3H).

Compound **S19B** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **112-4B** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-55%) to afford compound **S19B**. LCMS: $[M+H]^+$ = 783.6。^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.24 - 5.06 (m, 1H),

4.81 - 4.77 (m, 1H), 4.69 - 4.63 (m, 1H), 4.26 - 4.13 (m, 2H), 4.12 - 4.05 (m, 1H), 3.81 - 3.74 (m, 1H), 3.65 - 3.53 (m, 3H), 3.48 - 3.42 (m, 1H), 3.39 - 3.34 (m, 2H), 3.28 - 3.18 (m, 2H), 3.10 - 3.00 (m, 2H), 2.90 - 2.74 (m, 5H), 2.18 - 2.04 (m, 4H), 2.02 (s, 3H), 1.99 - 1.83 (m, 8H), 1.78 - 1.69 (m, 2H), 1.52 (s, 3H), 1.29 (s, 3H).

Example S20

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-((S)-1-methoxyethyl)phenyl)hexahydro-1H-pyrrolizine-3-carboxamide

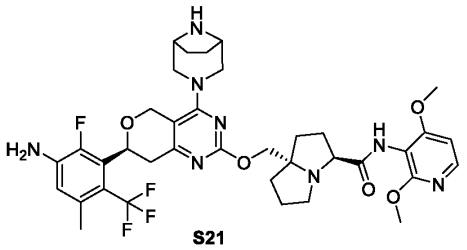


S20

Compound **S20** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with (S)-2-(1-methoxyethyl)aniline. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **S20**. LCMS: $[M+H]^+$ = 778.6。^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.65 (d, *J* = 8.0, 4.0 Hz, 1H), 7.40 - 7.18 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.11 (m, 1H), 4.81 - 4.77 (m, 1H), 4.71 - 4.64 (m, 1H), 4.60 - 4.52 (m, 1H), 4.28 - 4.11 (m, 3H), 4.05 - 3.97 (m, 1H), 3.71 - 3.54 (m, 3H), 3.49 - 3.44 (m, 1H), 3.27 - 3.20 (m, 4H), 3.13 - 3.06 (m, 2H), 2.91 - 2.81 (m, 2H), 2.25 - 2.03 (m, 5H), 2.01 (s, 3H), 2.00 - 1.85 (m, 5H), 1.83 - 1.73 (m, 2H), 1.41 (d, *J* = 4.0 Hz, 3H).

Example S21

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2,4-dimethoxypyridin-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide

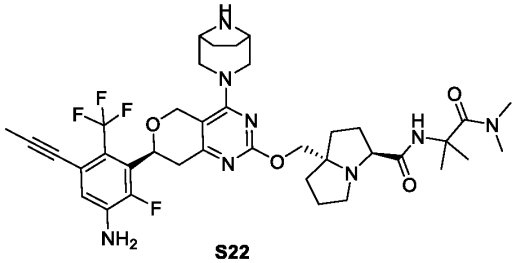


S21

Compound **S21** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine and intermediate **4-2** (CN 2024/083328) with 2,4-dimethoxypyridin-3-amine and intermediate **82-2B** (CN 2024/083328) respectively. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-70%) to afford compound **S21**. LCMS: $[M+H]^+$ = 757.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.99 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 5.22 - 5.11 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.25 - 4.06 (m, 3H), 4.03 - 3.97 (m, 1H), 3.90 (d, J = 8.0 Hz, 6H), 3.59 - 3.50 (m, 3H), 3.46 - 3.41 (m, 1H), 3.27 - 3.19 (m, 1H), 3.16 - 3.11 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.96 - 2.82 (m, 2H), 2.36 (q, J = 4.0 Hz, 3H), 2.25 - 2.06 (m, 3H), 2.05 - 1.89 (m, 5H), 1.88 - 1.75 (m, 3H), 1.74 - 1.65 (m, 1H).

Example S22

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



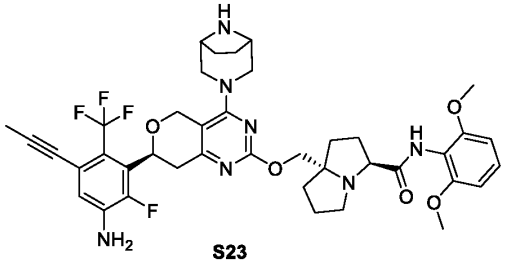
S22

Compound **S22** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-amino-N,N,2-trimethylpropanamide. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-60%) to afford compound **S22**. LCMS: $[M+H]^+$ = 757.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.79 (dd, J = 8.0, 4.0 Hz, 1H), 3.55 - 3.52 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 20.0, 12.0 Hz, 1H), 3.09 - 2.75 (m, 10H), 2.11 - 2.06 (m, 2H), 2.04 - 1.99 (m, 4H), 1.98 - 1.83 (m, 7H), 1.75 - 1.68 (m, 2H), 1.50 (s, 3H), 1.47 (s, 3H).

Example S23

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-

yl)oxy)methyl)-N-(2,6-dimethoxyphenyl)hexahydro-1H-pyrrolizine-3-carboxamide

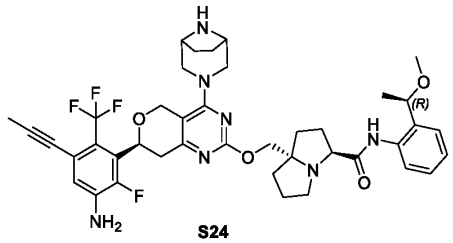


S23

Compound **S23** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 2,6-dimethoxyaniline. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-50%) to afford compound **S23**. LCMS: $[M+H]^+$ = 780.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.24 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 8.0 Hz, 1H), 4.04 - 4.00 (m, 1H), 3.80 (s, 6H), 3.56 - 3.53 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.14 (m, 2H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.93 (m, 1H), 2.86 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.24 - 2.19 (m, 1H), 2.14 - 2.06 (m, 2H), 2.05 - 1.97 (m, 7H), 1.93 - 1.68 (m, 5H).

Example S24

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-((R)-1-methoxyethyl)phenyl)hexahydro-1H-pyrrolizine-3-carboxamide



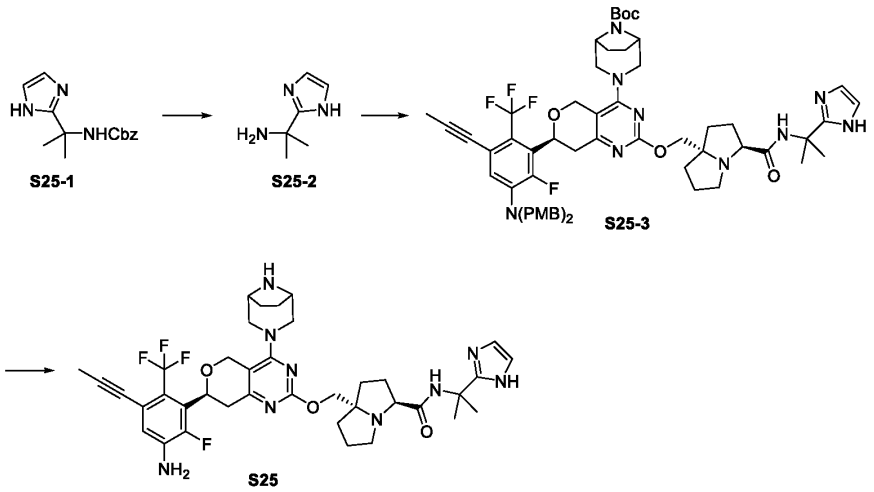
S24

Compound **S24** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (R)-2-(1-methoxyethyl)aniline. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S24**. LCMS: $[M+H]^+$ = 778.5 $[M+H]^+$。 ^1H NMR (400 MHz, CD_3OD) δ ppm 7.67 - 7.59 (m, 1H), 7.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.33 - 7.20 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.22 - 5.10 (m, 1H), 4.82 - 4.77 (m, 1H), 4.69 - 4.55 (m, 2H), 4.25 - 4.10 (m, 3H), 4.05 - 3.95 (m, 1H), 3.61 - 3.49 (m, 3H), 3.46 - 3.40 (m, 1H), 3.27 - 3.18 (m, 4H), 3.15 - 3.04 (m, 2H), 2.90 - 2.80 (m, 2H), 2.26 - 2.10 (m, 3H), 2.08 - 1.90 (m, 8H), 1.88 - 1.67 (m,

4H), 1.42 (d, J = 8.0 Hz, 3H).

Example S25

(3S,7aS)-N-(2-(1H-imidazol-2-yl)propan-2-yl)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step1：S25-2

To a solution of compound **S25-1** (40 mg, 0.36 mmol) in THF (5 mL) was added Pd/C (15 mg, 10% on Carbon (wetted with ca. 55% Water)). The mixture was stirred at 25 °C under H_2 balloon for 12 h The mixture was filtered by celite and concentrated in vacuum to afford compound **S25-2**. LCMS: $[M+H]^+$ = 126.06.

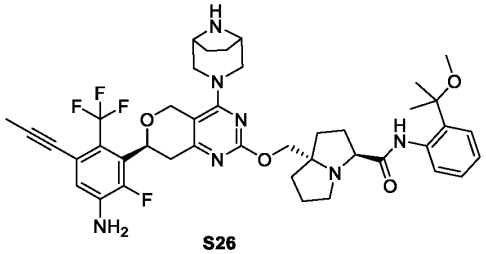
Step 2~3：S25

Compound **S25** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S25-2**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S25**. LCMS: $[M+H]^+$ = 752.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.95 - 6.85 (m, 3H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 - 4.77 (m, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.21 - 4.12 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.82 - 3.77 (m, 1H), 3.58 - 3.41 (m, 5H), 3.23 (dd, J = 16.0, 12.0 Hz, 1H), 3.06 (d, J = 12.0 Hz, 1H), 2.91 - 2.82 (m, 2H), 2.75 - 2.68 (m, 1H), 2.14 - 2.03 (m, 3H), 2.02 (s, 3H), 1.94 - 1.80 (m, 8H), 1.72 (s, 3H), 1.67 (s, 3H).

Example S26

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-

((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(2-methoxypropan-2-yl)phenyl)hexahydro-1H-pyrrolizine-3-carboxamide

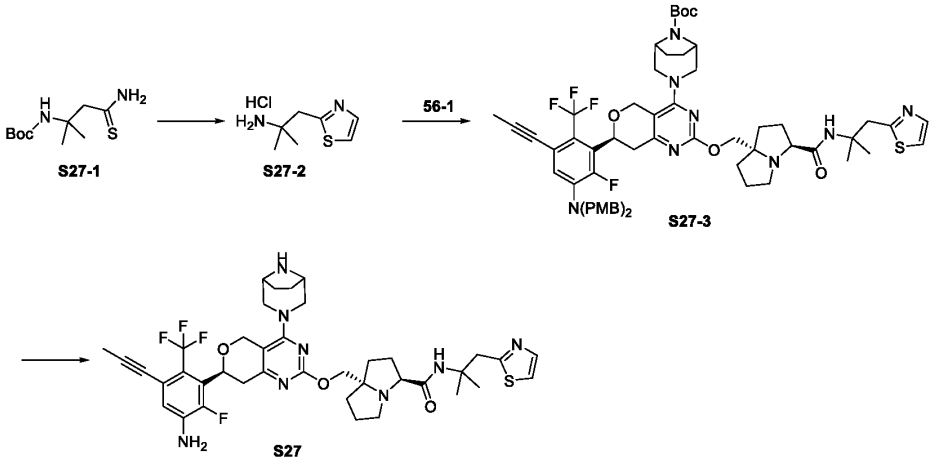


S26

Compound **S26** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 2-(2-methoxypropan-2-yl)aniline. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **S26**. LCMS: $[M+H]^+$ = 792.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.32 - 8.23(m, 1H), 7.34 - 7.26 (m, 2H), 7.14 -7.07 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.19 - 5.09 (m, 1H), 4.80 - 4.76 (m, 1H), 4.69 - 4.61 (m, 1H), 4.24 - 4.11 (m, 3H), 3.61 - 3.36 (m, 5H), 3.27 - 3.20 (m, 1H), 3.16 - 3.09 (m, 4H), 3.08 - 3.02 (m, 1H), 2.89 - 2.81 (m, 1H), 2.80 - 2.73 (m, 1H), 2.25 - 2.13 (m, 2H), 2.10 - 2.00 (m, 5H), 1.99 - 1.89 (m, 3H), 1.88 - 1.65 (m, 5H), 1.64 - 1.57 (m, 6H).

Example S27

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-methyl-1-(thiazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S27-2

A solution of compound **S27-1** (200 mg, 860.80 μmol), 2-chloroacetaldehyde (101.3 mg, 1.29

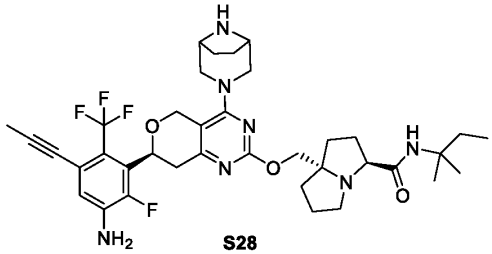
mmol) and calcium carbonate (86.2 mg, 860.80 μmol) in anhydrous EtOH (10 mL) was stirred for 24 hours at 80 °C. The reaction was filtered, the filtrate was concentrated under reduced pressure. The residue was redissolved in DCM (3 mL), then HCl (2 mL, 4 M in dioxane) was added. The resulting mixture was stirred for 1 hour at 25 °C. The reaction was concentrated under reduced pressure to afford crude compound **S27-2**. LCMS: $[M+H]^+$ = 157.1.

Step 2~3：S27

Compound **S27** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S27-2**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 50%-80%) to afford compound **S27**. LCMS: $[M+H]^+$ = 783.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.71 (d, *J* = 4.0 Hz, 1H), 7.48 (d, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.77 (s, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.11 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 1H), 3.75 - 3.69 (m, 1H), 3.52 - 3.49 (m, 3H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.29 (s, 1H), 3.20 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.75 (m, 3H), 2.20 - 2.08 (m, 2H), 2.01 (s, 3H), 2.00 - 1.82 (m, 8H), 1.76 - 1.65 (m, 2H), 1.48 (s, 3H), 1.29 (s, 3H).

Example S28

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(tert-pentyl)hexahydro-1H-pyrrolizine-3-carboxamide



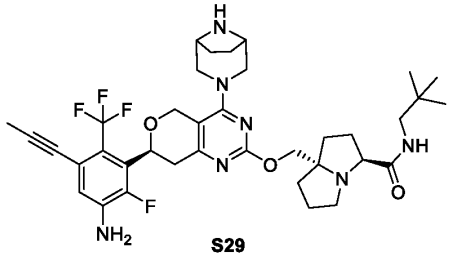
S28

Compound **S28** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-methylbutan-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **S28**. LCMS: $[M+H]^+$ = 714.5. ^1H NMR (400 MHz, CD_3OD) *δ* ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.81 - 4.77 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.21 - 4.13 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.77 - 3.71 (m, 1H), 3.58 - 3.51 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.92 (m, 1H), 2.88 - 2.82 (m, 1H), 2.80 - 2.73 (m, 1H), 2.15 - 2.06 (m, 2H), 2.05 - 1.99 (m, 4H), 1.94 -

1.79 (m, 8H), 1.76 - 1.67 (m, 3H), 1.30 (d, *J* = 12.0 Hz, 6H), 0.88 (t, J = 8.0 Hz, 3H).

Example S29

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-neopentylhexahydro-1H-pyrrolizine-3-carboxamide

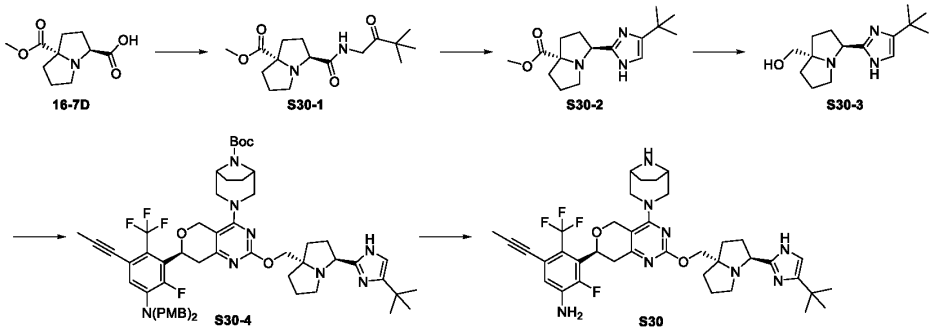


S29

Compound **S29** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2,2-dimethylpropan-1-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-80%) to afford compound **S29**. LCMS: $[M+H]^+$ = 714.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.19 - 5.12 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.20 - 4.11 (m, 2H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.55 - 3.49 (m, 3H), 3.44 - 3.38 (m, 1H), 3.25 - 3.17 (m, 1H), 3.06 - 3.04 (m, 2H), 3.03 - 3.01 (m, 1H), 2.96 - 2.90 (m, 1H), 2.88 - 2.81 (m, 1H), 2.79 - 2.72 (m, 1H), 2.16 - 2.08 (m, 2H), 2.05 - 1.97 (m, 5H), 1.95 - 1.87 (m, 4H), 1.86 - 1.79 (m, 2H), 1.77 - 1.65 (m, 2H), 0.93 (s, 9H).

Example S30

3-((S)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((3S,7aS)-3-(4-(tert-butyl)-1H-imidazol-2-yl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-7-yl)-2-fluoro-5-(prop-1-yn-1-yl)-4-(trifluoromethyl)aniline



Step 1: S30-1

To a solution of compound **16-7D** (CN 2024/083328) (300 mg, 1.41 mmol) in DMF (5 mL) was added HATU (1.07 g, 2.81 mmol), DIEA (545.51 mg, 4.22 mmol) and 1-amino-3,3-dimethylbutan-2-one hydrochloride (320.01 mg, 2.11 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 6 hours. Water (25 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (DCM : MeOH = 20:1) to afford compound **S30-1**. LCMS: $[M+H]^+$=311.3 .

Step 2：S30-2

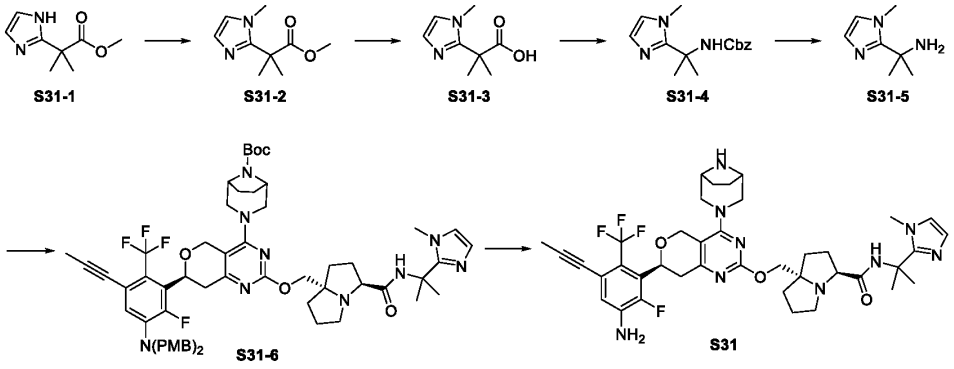
To a solution of compound **S30-1** (120 mg, 0.39 mmol) in toluene (10 mL) was added NH_4OAc (1.19 g, 15.46 mmol) at 25 °C. The reaction mixture was stirred at 110 °C for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM : MeOH = 20:1) to afford compound **S30-2**. LCMS: $[M+H]^+$ = 292.1.

Steps 3~5: S30

Compound **S30** was prepared analogous to compound **16D** (CN 2024/083328), replacing compound **16-8D** (CN 2024/083328) with compound **S30-2**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **S30**. LCMS: $[M+H]^+$ = 723.5. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 5.21 - 5.09 (m, 1H), 4.82 - 4.78 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.24 - 4.07 (m, 3H), 3.92 (t, *J* = 8.0 Hz, 1H), 3.64 - 3.51 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.79 (m, 3H), 2.28 - 2.15 (m, 3H), 2.05 - 1.97 (m, 5H), 1.91 - 1.68 (m, 7H), 1.28 (s, 9H).

Example S31

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(1-methyl-1H-imidazol-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S31-2

To a solution of compound **S31-1** (2 g, 11.89 mmol) in THF (20 mL) was added NaH (285.36 mg, 11.89 mmol, 60% purity) at 0 °C. The mixture was stirred at 0 °C for 0.5 hours and then iodomethane (1.69 g, 11.89 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was quenched with sat.NH_4Cl (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (DCM : MeOH = 20:1) to afford compound **S31-2**. LCMS: $[M+H]^+$ = 183.2.

Step 2: S31-3

To a solution of compound **S31-2** (800 mg, 4.39 mmol) in EtOH (8 mL) was added NaOH (959.93 mg, 24 mmol) in H_2O (24 mL) at 25 °C. The mixture was stirred at 40 °C for 3 hours. The mixture was adjusted to pH = 6 with 1 N HCl and concentrated to remove solvent. The crude product was duilted with MeOH (20 mL), filtered and the filter cake was washed with MeOH (20 mL).The filtrate was concentrated in vacuum to afford compound **S31-3**. LCMS: $[M+H]^+$ = 169.2.

Step 3: S31-4

To a solution of compound **S31-3** (150 mg, 0.89 mmol) in Toluene (6 mL) was added TEA (126 mg, 1.25 mmol) and DPPA (319 mg, 1.16 mmol) at 25 °C. The mixture was stirred at 80 °C for 2 hours and then BnOH (144 mg, 1.34 mmol) was added. The mixture was stirred at 80 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by flash chromatography (DCM : MeOH = 10:1) to afford compound **S31-4**. LCMS: $[M+H]^+$ = 274.2.

Step 4: S31-5

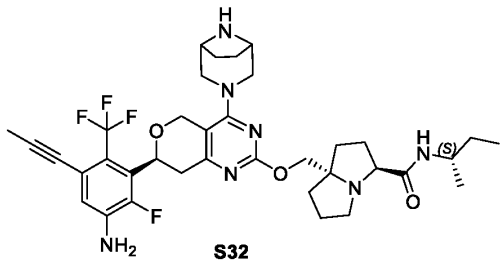
To a solution of compound **S31-4** (100 mg, 0.36 mmol) in THF (5 mL) was added Pd/C (38 mg, 10% purtiy). The mixture was stirred at 25 °C under H_2 ballon for 12 hours. The mixture was filtered by celite and concentrated in vacuum to afford compound **S31-5**. LCMS: $[M+H]^+$ = 140.1.

Steps 5~6: S31

Compound **S31** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S31-5**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S31**. LCMS: $[M+H]^+$ = 766.6. ^1H NMR (400 MHz, CD_3OD) δ 6.96 - 6.86 (m, 2H), 6.80 (d, *J* = 4.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 - 4.77 (m, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.21 - 4.12 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.86 - 3.80 (m, 1H), 3.71 (s, 3H), 3.62 - 3.57 (m, 2H), 3.55 (d, *J* = 16.0 Hz, 1H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.90 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.79 - 2.71 (m, 1H), 2.12 - 2.03 (m, 3H), 2.02 (s, 3H), 1.96 - 1.81 (m, 7H), 1.77 (s, 3H), 1.74 - 1.65 (m, 2H), 1.62 (s, 3H).

Example S32

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-sec-butyl)hexahydro-1H-pyrrolizine-3-carboxamide



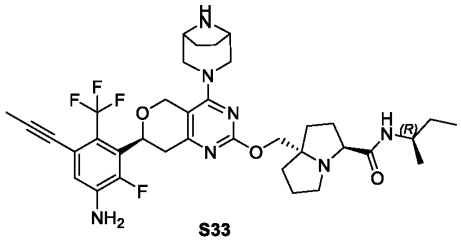
S32

Compound **S32** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (S)-butan-2-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S32**. LCMS: $[M+H]^+$ = 700.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.81 - 4.77 (m, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.11 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.86 - 3.78 (m, 1H), 3.77 - 3.71 (m, 1H), 3.56 - 3.49 (m, 3H), 3.45 - 3.38 (m, 1H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.95 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.80 - 2.70 (m, 1H), 2.15 - 2.06 (m, 2H), 2.01 (s, 3H), 2.00 - 1.79 (m, 8H), 1.78 - 1.64 (m, 2H), 1.54 - 1.44 (m, 2H), 1.14 (d, *J* = 8.0 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 3H).

Example S33

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-

((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-sec-butyl)hexahydro-1H-pyrrolizine-3-carboxamide

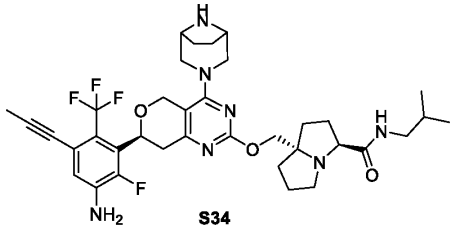


S33

Compound **S33** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (R)-butan-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 42%-42%) to afford compound **S33**. LCMS: $[M+H]^+$ = 700.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.18 - 5.12 (m, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.85 - 3.77 (m, 1H), 3.76 - 3.71 (m, 1H), 3.57 - 3.50 (m, 3H), 3.45 - 3.40 (m, 1H), 3.26 - 3.18 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.96 - 2.90 (m, 1H), 2.88 - 2.82 (m, 1H), 2.81 - 2.73 (m, 1H), 2.13 - 2.07 (m, 2H), 2.04 - 2.00 (m, 4H), 1.99 - 1.87 (m, 5H), 1.86 - 1.80 (m, 2H), 1.77 - 1.67 (m, 2H), 1.55 - 1.47 (m, 2H), 1.13 (d, J = 8.0 Hz, 3H), 0.94 (t, J = 8.0 Hz, 3H).

Example S34

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-isobutylhexahydro-1H-pyrrolizine-3-carboxamide



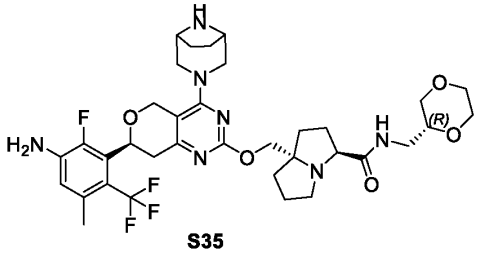
S34

Compound **S34** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-methylpropan-1-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 42%-72%) to afford compound **S34**. LCMS: $[M+H]^+$ = 700.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.20 - 5.11 (m, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.19 - 4.11 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.80 - 3.73 (m, 1H),

3.57 - 3.50 (m, 3H), 3.45 - 3.39 (m, 1H), 3.26 - 3.17 (m, 1H), 3.07 - 2.97 (m, 4H), 2.95 - 2.89 (m, 1H), 2.88 - 2.82 (m, 1H), 2.79 - 2.72 (m, 1H), 2.14 - 2.07 (m, 2H), 2.03 - 1.99 (m, 4H), 1.97 - 1.89 (m, 4H), 1.85 - 1.69 (m, 5H), 0.94 (d, J = 4.0 Hz, 6H).

Example S35

(3S,7aS)-N-(((R)-1,4-dioxan-2-yl)methyl)-7a-((((S)-7-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizine-3-carboxamide

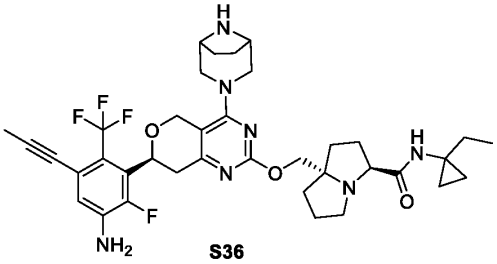


S35

Compound **S35** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine and intermediate **4-2** (CN 2024/083328) with (R)-(1,4-dioxan-2-yl)methanamine hydrochloride and intermediate **82-2B** (CN 2024/083328) respectively. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (10 mM NH_4HCO_3); Gradient: (ACN): 20%-78%) to afford compound **S35**. LCMS: $[M+H]^+$ = 720.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.68 (d, J = 8.0 Hz, 1H), 5.17 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, J = 8.0 Hz, 1H), 3.79 - 3.73 (m, 3H), 3.69 - 3.62 (m, 3H), 3.59 - 3.51 (m, 4H), 3.42 (d, J = 12.0 Hz, 1H), 3.35 - 3.32 (m, 1H), 3.29 - 3.28 (m, 1H), 3.25 - 3.13 (m, 2H), 3.04 (d, J = 12.0 Hz, 1H), 2.96 - 2.90 (m, 1H), 2.85 (dd, J = 16.0, 4.0 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.38 - 2.34 (m, 3H), 2.13 - 2.06 (m, 2H), 2.03 - 1.82 (m, 8H), 1.76 - 1.66 (m, 2H).

Example S36

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-ethylcyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide

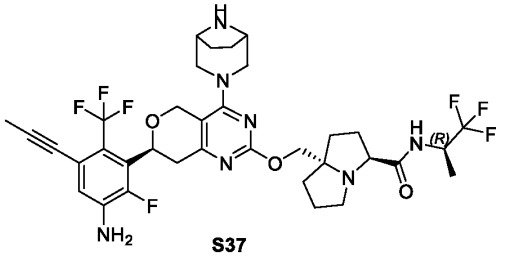


S36

Compound **S36** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 1-ethylcyclopropan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S36**. LCMS: $[M+H]^+$ = 712.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.17 - 4.13 (m, , 2H), 4.04 (d, *J* = 8.0 Hz, 1H), 3.70 - 3.67 (m, 1H), 3.58 - 3.52 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.06 (d, *J* = 16.0 Hz, 1H), 2.91 - 2.73 (m, 3H), 2.12 - 1.98 (m, 7H), 1.96 - 1.90 (m, 6H), 1.77 - 1.68 (m, 2H), 1.63 - 1.55 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 3H), 0.71 - 0.68 (m, 2H), 0.65 - 0.62 (m, 2H).

Example S37

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-1,1,1-trifluoropropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

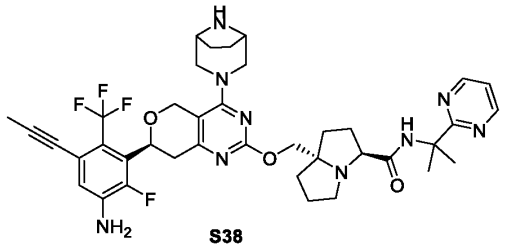


S37

Compound **S37** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (*R*)-1,1,1-trifluoropropan-2-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-80%) to afford compound **S37**. LCMS: $[M+H]^+$ = 740.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.69 - 4.62 (m, 2H), 4.17 - 4.13 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.81 - 3.77 (m, 1H), 3.54 - 3.51 (m, 3H), 3.42 (d, *J* = 8.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.89 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.75 - 2.68 (m, 1H), 2.14 - 2.07 (m, 2H), 2.05 - 1.98 (m, 5H), 1.95 - 1.82 (m, 6H), 1.77 - 1.66 (m, 2H), 1.33 (d, *J* = 8.0 Hz, 3H).

Example S38

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-(pyrimidin-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

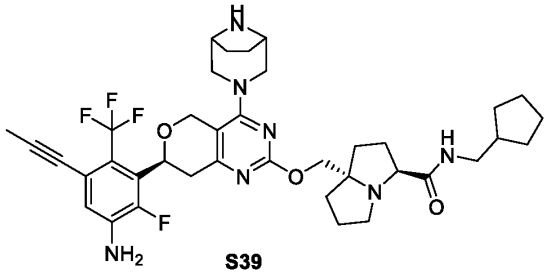


S38

Compound **S38** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 2-(pyrimidin-2-yl)propan-2-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-52%) to afford compound **S38**. LCMS: $[M+H]^+$ = 764.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.72 (d, *J* = 4.0 Hz, 2H), 7.30 (t, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.22 - 4.13 (m, 2H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.90 - 3.83 (m, 1H), 3.64 - 3.53 (m, 3H), 3.45 (d, *J* = 16.0 Hz, 1H), 3.24 - 3.19 (m, 1H), 3.10 - 3.03 (m, 2H), 2.86 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.80 - 2.74 (m, 1H), 2.15 - 2.04 (m, 3H), 2.02 (s, 3H), 1.97 - 1.83 (m, 7H), 1.71 (d, *J* = 16.0 Hz, 8H).

Example S39

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(cyclopentylmethyl)hexahydro-1H-pyrrolizine-3-carboxamide



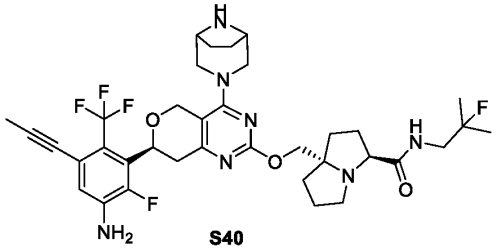
S39

Compound **S39** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with cyclopentylmethanamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 50%-70%) to afford compound **S39**. LCMS: $[M+H]^+$ = 726.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.54 - 3.50 (m, 2H), 3.41 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.25 - 3.20 (m, 1H), 3.18 - 3.12 (m, 2H), 3.03 (d, *J* = 12.0 Hz, 1H), 2.99 (s, 1H), 2.93 - 2.88 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.77 - 2.71 (m, 1H), 2.14 - 2.04 (m, 3H), 2.01 (s, 3H), 1.99 - 1.89 (m, 5H), 1.87 - 1.73 (m, 5H), 1.72 - 1.51

(m, 6H), 1.29 - 1.20 (m, 2H).

Example S40

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-fluoro-2-methylpropyl)hexahydro-1H-pyrrolizine-3-carboxamide

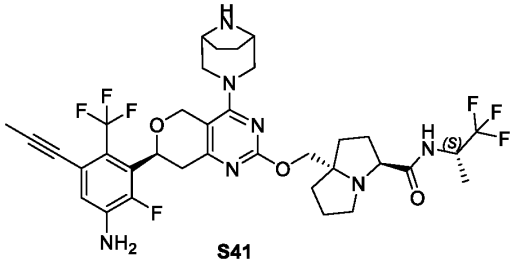


S40

Compound **S40** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 2-fluoro-2-methylpropan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S40**. LCMS: $[M+H]^+$ = 718.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.84 - 3.81 (m, 1H), 3.57 - 3.50 (m, 3H), 3.46 - 3.36 (m, 3H), 3.25 - 3.18 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.91 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.80 - 2.73 (m, 1H), 2.15 - 2.07 (m, 2H), 2.06 - 1.98 (m, 5H), 1.96 - 1.86 (m, 4H), 1.85 - 1.79 (m, 2H), 1.78 - 1.65 (m, 2H), 1.37 (d, *J* = 4.0 Hz, 3H), 1.32 (d, *J* = 4.0 Hz, 3H).

Example S41

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-1,1,1-trifluoropropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



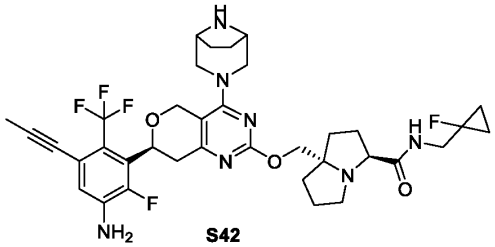
S41

Compound **S41** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (*S*)-1,1,1-trifluoropropan-2-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm,

5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 20%-60%) to afford compound **S41**. LCMS: $[M+H]^+$ = 740.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.69 - 4.61 (m, 2H), 4.17 - 4.12 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.81 - 3.77 (m, 1H), 3.56 - 3.51 (m, 3H), 3.42 (d, *J* = 8.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.89 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.76 - 2.70 (m, 1H), 2.13 - 1.99 (m, 7H), 1.98 - 1.82 (m, 6H), 1.78 - 1.67 (m, 2H), 1.33 (d, *J* = 8.0 Hz, 3H).

Example S42

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-fluorocyclopropyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide

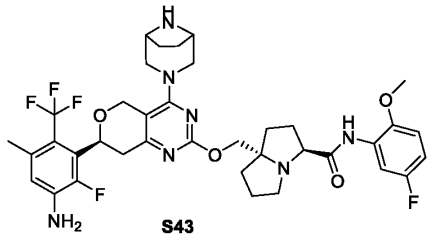


S42

Compound **S42** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1-fluorocyclopropyl)methanamine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 50%-65%) to afford compound **S42**. LCMS: $[M+H]^+$ = 716.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.83 - 3.78 (m, 1H), 3.72 - 3.62 (m, 1H), 3.58 - 3.49 (m, 4H), 3.43 - 3.39 (m, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.03 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.92 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.15 - 2.07 (m, 2H), 2.05 - 1.97 (m, 5H), 1.96 - 1.86 (m, 4H), 1.85 - 1.80 (m, 2H), 1.77 - 1.66 (m, 2H), 1.05 - 0.97 (m, 2H), 0.78 - 0.72 (m, 2H).

Example S43

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(5-fluoro-2-methoxyphenyl)hexahydro-1H-pyrrolizine-3-carboxamide

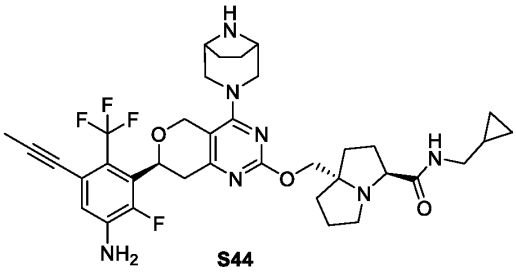


S43

Compound **S43** was prepared analogous to compound **82B** (CN 2024/083328), replacing intermediate **20-2D** (CN 2024/083328) with intermediate **81-3** (CN 2024/083328). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-65%) to afford compound **S43**. LCMS: $[M+H]^+$ = 744.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.04 - 7.91 (m, 1H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.86 - 6.76 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.09 (m, 2H), 4.06 - 3.99 (m, 1H), 3.88 (s, 3H), 3.59 - 3.51 (m, 3H), 3.46 - 3.40 (m, 1H), 3.28 - 3.19 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.01 - 2.97 (m, 1H), 2.91 - 2.82 (m, 1H), 2.80 - 2.71 (m, 1H), 2.36 (q, *J* = 4.0 Hz, 3H), 2.25 - 2.13 (m, 2H), 2.07 - 2.00 (m, 2H), 1.98 - 1.89 (m, 4H), 1.87 - 1.81 (m, 2H), 1.78 - 1.67 (m, 2H).

Example S44

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(cyclopropylmethyl)hexahydro-1H-pyrrolizine-3-carboxamide



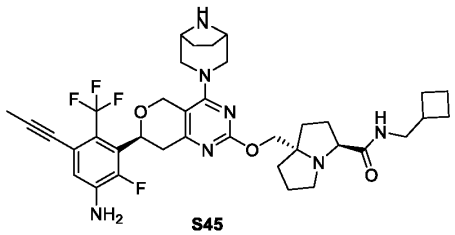
S44

Compound **S44** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with cyclopropylmethanamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S44**. LCMS: $[M+H]^+$ = 698.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.12 (m, 2H), 4.07 - 4.02 (m, 1H), 3.79 - 3.73 (m, 1H), 3.55 - 3.48 (m, 3H), 3.44 - 3.38 (m, 1H), 3.25 - 3.18 (m, 1H), 3.15 - 3.09 (m, 1H), 3.06 - 3.01 (m, 2H), 2.95 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.79 - 2.70 (m, 1H), 2.14 - 2.07 (m, 2H), 2.02 (s, 3H), 2.00

- 1.86 (m, 6H), 1.85 - 1.79 (m, 2H), 1.76 - 1.65 (m, 2H), 1.05 - 0.94 (m, 1H), 0.55 - 0.46 (m, 2H), 0.26 - 0.19 (m, 2H).

Example S45

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(cyclobutylmethyl)hexahydro-1H-pyrrolizine-3-carboxamide

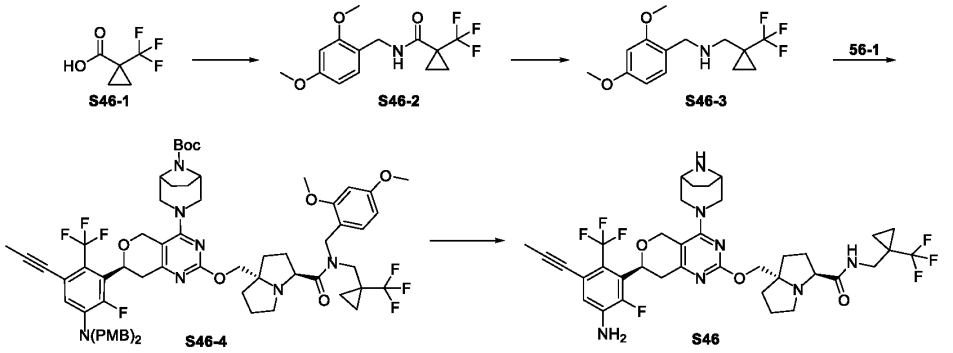


S45

Compound **S45** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with cyclobutylmethanamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S45**. LCMS: $[M+H]^+$ = 712.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.77 - 3.70 (m, 1H), 3.54 - 3.47 (m, 3H), 3.45 - 3.39 (m, 1H), 3.29 - 3.23 (m, 1H), 3.22 - 3.15 (m, 2H), 3.05 - 2.98 (m, 1H), 2.92 - 2.80 (m, 2H), 2.78 - 2.68 (m, 1H), 2.57 - 2.46 (m, 1H), 2.13 - 2.04 (m, 4H), 2.01 (s, 3H), 1.99 - 1.79 (m, 10H), 1.77 - 1.66 (m, 4H).

Example S46

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-(trifluoromethyl)cyclopropyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S46-2

To a stirred solution of compound **S46-1** (1 g, 6.49 mmol) in DCM (5 mL) was added (2,4-dimethoxyphenyl)methanamine (1.09 g, 6.49 mmol), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (2.19 g, 7.79 mmol) and N-methylimidazole (1.07 g, 12.98 mmol) at 25 °C. The reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 20:1) to afford compound **S46-2**. LCMS: $[M+H]^+$ = 304.1.

Step 2: S46-3

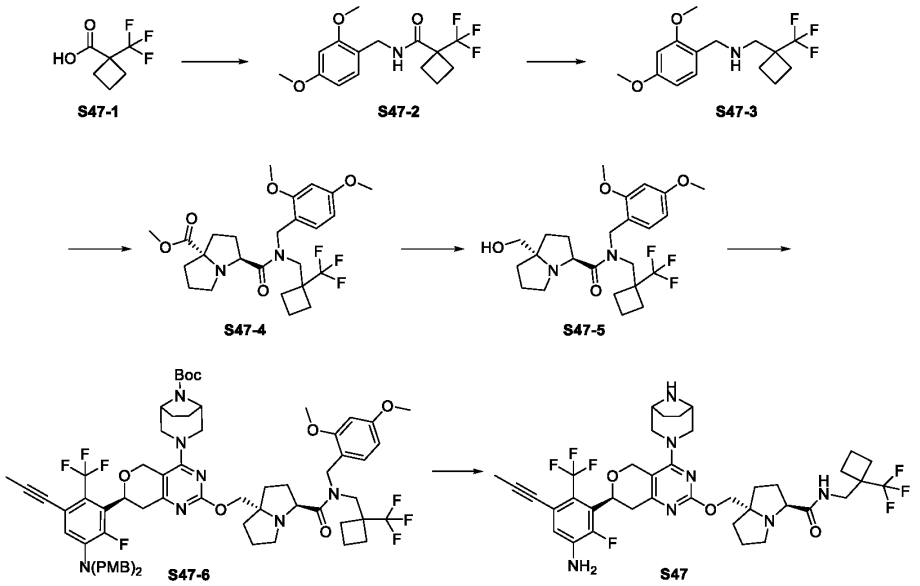
To a stirred solution of compound **S46-2** (500 mg, 1.65 mmol) in dry THF (1 mL) was added $LiAlH_4$ (3.3 mL， 8.24 mmol, 2.5 M in THF) at 0 °C. The reaction was stirred at 60 °C for 12 hours. The reaction was quenched with water (1 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **S46-3**. LCMS: $[M+H]^+$ = 290.1.

Steps 3~4：S46

Compound **S46** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S46-3**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S46**. LCMS: $[M+H]^+$ = 766.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.14 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.79 - 3.76 (m, 1H), 3.59 - 3.42 (m, 6H), 3.25 - 3.18 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.91 (m, 1H), 2.85 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.14 - 2.07 (m, 2H), 2.05 - 1.98 (m, 5H), 1.96 - 1.82 (m, 6H), 1.78 - 1.67 (m, 2H), 1.01 - 0.95 (m, 2H), 0.91 - 0.85 (m, 2H).

Example S47

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-(trifluoromethyl)cyclobutyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S47-2

To a stirred solution of compound **S47-1** (1 g, 5.95 mmol) and (2,4-dimethoxyphenyl)methanamine (1.19 g, 7.14 mmol) in DCM (10 mL) was added DIPEA (768.78 mg, 5.95 mmol, 1.04 mL) and HATU (2.26 g, 5.95 mmol) at 25 °C. The reaction was stirred at 25 °C for 2 hours. The reaction was quenched with water (5 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **S47-2**. LCMS: $[M+H]^+ = 318.4$.

Step 2: S47-3

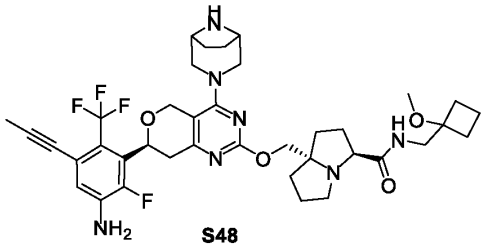
To a stirred solution of compound **S47-2** (500 mg, 1.58 mmol) in dry THF (1 mL) was added $LiAlH_4$ (3.15 mL， 7.88 mmol, 2.5 M in THF) at 0 °C. The reaction was stirred at 60 °C for 12 hours. The reaction was quenched with water (1 mL), extracted wtih EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **S47-3**. LCMS: $[M+H]^+ = 304.1$.

Steps 3~4：S47

Compound **S47** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with intermediate **S47-3**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S47**. LCMS: $[M+H]^+$ = 780.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.83 - 3.79 (m, 1H), 3.59 (s, 2H), 3.56 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.96 - 2.91 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.31 - 2.21 (m, 2H), 2.15 - 2.00 (m, 10H), 1.98 - 1.89 (m, 5H), 1.86 - 1.79 (m, 2H), 1.78 - 1.66 (m, 2H).

Example S48

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-methoxycyclobutyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide

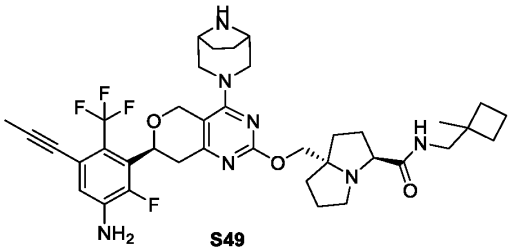


S48

Compound **S48** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1-methoxycyclobutyl)methanamine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 20%-60%) to afford compound **S48**. LCMS: $[M+H]^+$ = 742.6. ^1H NMR (400 MHz, CD_3OD) *δ* ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.83 - 3.79 (m, 1H), 3.59 - 3.51 (m, 4H), 3.47 - 3.40 (m, 2H), 3.25 - 3.18 (m, 4H), 3.04 (d, *J* = 16.0 Hz, 1H), 2.97 - 2.92 (m, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.76 - 2.69 (m, 1H), 2.17 - 2.09 (m, 4H), 2.04 - 1.96 (m, 5H), 1.95 - 1.86 (m, 6H), 1.85 - 1.80 (m, 2H), 1.78 - 1.61 (m, 4H).

Example S49

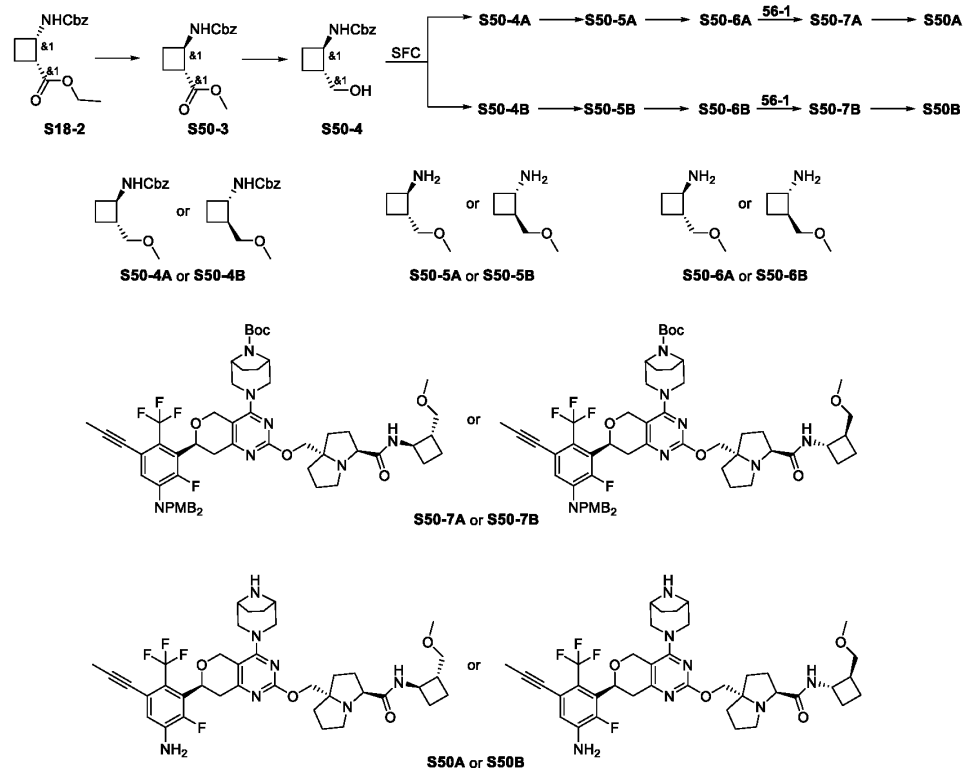
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-methylcyclobutyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



S49

Compound **S49** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1-methylcyclobutyl)methanamine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 48%-78%) to afford compound **S49**. LCMS: $[M+H]^+$ = 726.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.14 (m, 2H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.83 - 3.80 (m, 1H), 3.65 - 3.51 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.16 (m, 3H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.91 (m, 1H), 2.85 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.80 - 2.73 (m, 1H), 2.16 - 2.08 (m, 2H), 2.06 - 1.99 (m, 5H), 1.96 - 1.83 (m, 10H), 1.78 - 1.66 (m, 4H), 1.14 (s, 3H).

Example S50A and S50B
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1S,2S)-2-(methoxymethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide or
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1R,2R)-2-(methoxymethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S50-3

To a solution of compound **S18-2** (4.0 g, 14.42 mmol) in MeOH (80 mL) was added MeONa (10.4 g, 57.70 mol, 30% purity in MeOH) at 25 °C. The mixture was stirred at 50 °C for 4 hours. Acetic acid was added above reaction at 0 °C then stirred for 30 mins. The reaction solution was quenched with water (200 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 3:1) to afford compound **S50-3**. LCMS: $[M+H]^+ = 264.2$.

Step 2: S50-4 and S50-4A & S50-4B

To a solution of compound **S50-3** (2.5 g, 9.50 mmol) in THF (30 mL) was added $LiBH_4$ (399.23 mg, 19 mmol) and $NaBH_4$ (818.54 mg, 21.64 mmol) at 25 °C. The mixture was stirred at 25 °C for 5 hours. The mixture was quenched with sat. NH_4Cl (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE: EtOAc = 1:1) to afford compound **S50-4**. LCMS: $[M+H]^+ = 236.1$. Chiral Separation of Compound **S50-4** by SFC (DAICEL CHIRALPAK®IC-10, 25*250mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: [IPA+(0.05%)DEA]; B%, 30%) to obtain compounds **S50-4A** and **S50-4B**. SFC Analysis methods

(chromatographic column: DAICEL CHIRALPAK®IC-3 (3.0*100mm, 3μm); Mobile phase: A: Supercritical CO_2; B: (IPA +(0.05%) DEA, 5% -40%). Compound **S50-4A,** Rt =3.125 mins, ee: 100%, LCMS: $[M+H]^+$ = 236.1; compound **S50-4B**, Rt =3.482 mins, ee :97.84%, LCMS: $[M+H]^+$ = 236.1.

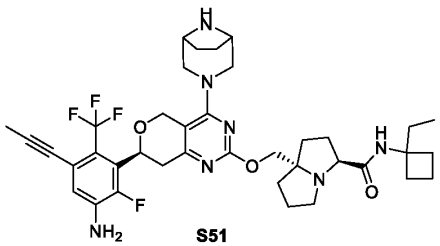
Steps 3~6：S50A

Compound **S50A** was prepared analogous to compound **S18A**, replacing intermediate **S18-4A** with intermediate **S50-4A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-75%) to afford Compound **S50A**. MS m/z = 742.5 $[M+H]^+$。 ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.09 (m, 3H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.53 - 3.48 (m, 3H), 3.45 - 3.37 (m, 3H), 3.32 (s, 3H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.94 - 2.82 (m, 2H), 2.77 - 2.69 (m, 1H), 2.51 - 2.41 (m, 1H), 2.23 - 2.15 (m, 1H), 2.14 - 2.05 (m, 2H), 2.04 - 1.80 (m, 13H), 1.76 - 1.65 (m, 2H), 1.58 - 1.47 (m, 1H).

Compound **S50B** was prepared analogous to compound **S50A**, replacing intermediate **S50-4A** with intermediate **S50-4B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-75%) to afford Compound **S50B**. MS m/z = 742.5 $[M+H]^+$。 ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.02 (m, 4H), 3.74 - 3.68 (m, 1H), 3.56 - 3.49 (m, 3H), 3.44 - 3.36 (m, 3H), 3.32 (s, 3H), 3.26 - 3.18 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.91 - 2.81 (m, 2H), 2.75 - 2.68 (m, 1H), 2.52 - 2.43 (m, 1H), 2.24 - 2.17 (m, 1H), 2.14 - 2.06 (m, 2H), 2.02 - 1.65 (m, 15H), 1.58 - 1.50 (m, 1H).

Example S51

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-ethylcyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



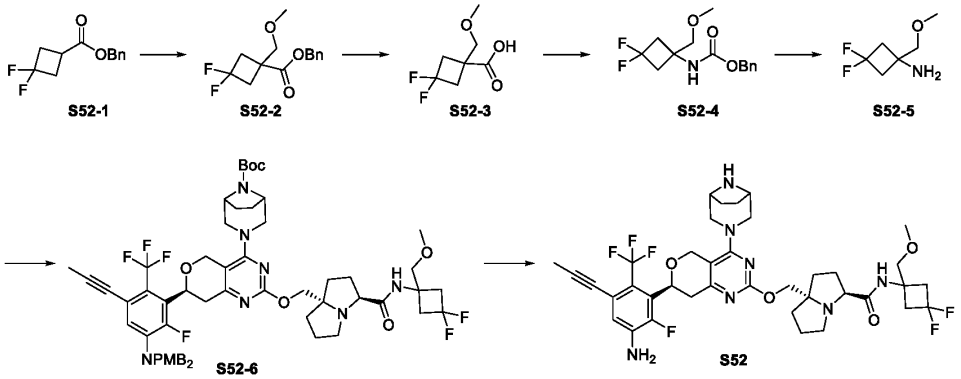
S51

Compound **S51** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 1-ethylcyclobutan-1-amine. The crude product was

purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-80%) to afford Compound **S51**. LCMS: $[M+H]^+$ = 726.5. ^1H NMR (400 MHz,CD_3OD) δ ppm δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.20 - 4.13 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.58 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.98 - 2.92 (m, 1H), 2.88 - 2.77 (m, 2H), 2.26 - 2.16 (m, 2H), 2.14 - 2.04 (m, 4H), 2.02 (s, 4H), 1.99 - 1.90 (m, 6H), 1.88 - 1.77 (m, 5H), 1.76 - 1.65 (m, 2H), 0.86 (t, *J* = 8.0 Hz, 3H).

Example S52

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3,3-difluoro-1-(methoxymethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S52-2

To a mixture of **S52-1** (600 mg, 2.65 mmol) and bromo(methoxy)methane (662.89 mg, 5.3 mmol) in THF (10 mL) was added LiHMDS (5.30 mmol, 5.30 mL, 1 M in THF) at -78 °C. The resulting mixture was stirred for 16 hours at 25 °C under N_2 atmosphere. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE : EtOAc = 15:1) to afford compound **S52-2**. ^1H NMR (400 MHz, CDCl3) δ 7.42 – 7.31 (m, 5H), 5.21 (s, 2H), 3.67 (s, 2H), 3.35 (s, 3H), 3.11-2.90 (m, 2H), 2.73-2.52 (m, 2H).

Step 2: S52-3

To a mixture of compound **S52-2** (280 mg, 1.04 mmol) in THF (10 mL) was added Pd/C (110.25 mg, 10% purity). The resulting mixture was stirred for 16 hours at 25 °C under H_2 ballon. The

resulting mixture was filtered, the filter cake was washed with EtOAc, the filtrate was concentrated under reduced pressure to afford compound **S52-3**. LCMS: $[M-H]^-$ = 179.1.

Step 3: S52-4

To a mixture of compound **S52-3** (170 mg, 943.66 μmol) in toluene (5 mL) was added DPPA (337.60 mg, 1.23 mmol) and TEA (133.68 mg, 1.32 mmol) at 25 °C. The mixture was stirred for 2 hours at 80 °C under N_2 atmosphere, Then BnOH (153.07 mg, 1.42 mmol) was added and the was stirred for 2 hours at 80 °C under N_2 atmosphere. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S52-4**. LCMS: $[M+H]^+$ = 286.3.

Step 4: S52-5

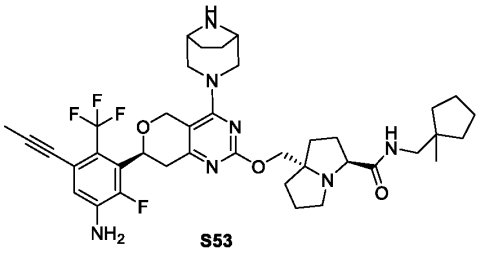
To a mixture of compound **S52-4** (200 mg, 701.05 μmol) in THF (10 mL) was added Pd/C (74.61 mg, 10% purtiy). The resulting mixture was stirred for 16 hours at 25 °C under H_2 ballon. The resulting mixture was filtered, the filter cake was washed with EtOAc, the filtrate was concentrated under reduced pressure to afford compound **S52-5**. LCMS: $[M+H]^+$ = 152.2.

Steps 5~6: S52

Compound **S52** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S52-5**. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-60%) to afford compound **S52**. LCMS: $[M+H]^+$ = 778.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.12 (m, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.78 - 3.73 (m, 1H), 3.61 - 3.49 (m, 5H), 3.43 - 3.39 (m, 1H), 3.37 (s, 3H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.07 - 3.01 (m, 1H), 3.00 - 2.93 (m, 1H), 2.88 - 2.70 (m, 6H), 2.14 - 2.06 (m, 2H), 2.02 (s, 3H), 2.00 - 1.78 (m, 8H), 1.76 - 1.64 (m, 2H).

Example S53

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-methylcyclopentyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide

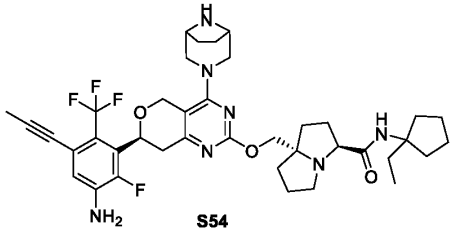


S53

Compound **S53** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1-methylcyclopentyl) methanamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-80%) to afford Compound **S53**. LCMS: $[M+H]^+$ = 740.6. ^1H NMR (400 MHz, CD_3OD) δ ppm δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.57 - 3.49 (m, 3H), 3.45 - 3.39 (m, 1H), 3.26 - 3.19 (m, 1H), 3.18 - 3.10 (m, 2H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.96 - 2.90 (m, 1H), 2.88 - 2.81 (m, 1H), 2.79 - 2.71 (m, 1H), 2.16 - 2.07 (m, 2H), 2.04 - 1.96 (m, 5H), 1.95 - 1.80 (m, 6H), 1.78 - 1.64 (m, 6H), 1.55 - 1.47 (m, 2H), 1.38 - 1.29 (m, 2H), 1.01 (s, 3H).

Example S54

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-ethylcyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



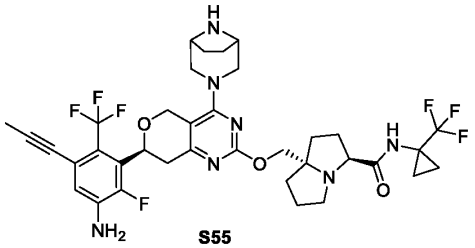
S54

Compound **S54** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 1-ethylcyclopentylamine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-70%) to afford compound **S54**. LCMS: $[M+H]^+$= 740.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.81 - 4.78 (m, 1H), 4.67 - 4.62 (m, 1H), 4.19 - 4.11 (m, 2H), 4.08 - 4.03 (m, 1H), 3.76 - 3.72 (m, 1H), 3.56 - 3.49 (m, 3H), 3.45 - 3.38 (m, 1H), 3.27 - 3.17 (m, 1H), 3.07 - 3.01 (m, 1H), 2.97 - 2.90 (m, 1H), 2.88 - 2.82 (m, 1H), 2.81 - 2.73 (m, 1H), 2.15 - 2.04 (m, 3H), 2.01 (s, 3H), 2.00 - 1.86 (m, 8H),

1.85 - 1.79(m, 2H), 1.78 - 1.71 (m, 3H), 1.70 - 1.56 (m, 6H), 0.91 - 0.84 (m, 3H).

Example S55

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-(trifluoromethyl)cyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide

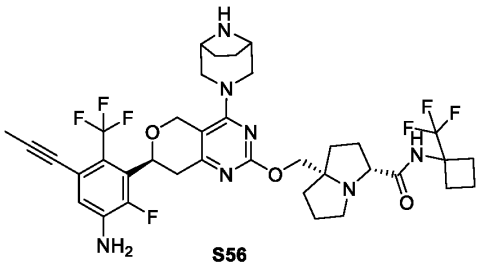


S55

Compound **S55** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride with 1-(trifluoromethyl)cyclopropan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford Compound **S55**. LCMS: $[M+H]^+$ = 752.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.17 - 4.12 (m, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.75 - 3.71 (m, 1H), 3.55 - 3.51 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.86 (m, 2H), 2.75 - 2.68 (m, 1H), 2.13 - 2.06 (m, 2H), 2.03 - 1.98 (m, 5H), 1.96 - 1.88 (m, 4H), 1.86 - 1.81 (m, 2H), 1.76 - 1.67 (m, 2H), 1.31 - 1.25 (m, 2H), 1.15 - 1.03 (m, 2H).

Example S56

(3R,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-(trifluoromethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



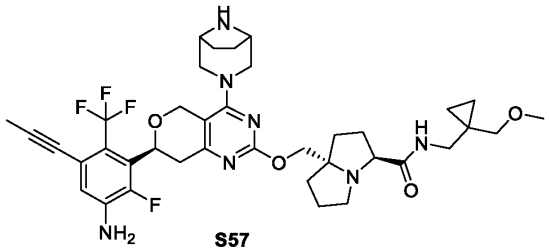
S56

Compound **S56** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-

difluorocyclopentanamine hydrochloride with 1-(trifluoromethyl)cyclobutan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-80%) to afford compound **S56**. LCMS: $[M+H]^+$ = 766.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 8.0 Hz, 1H), 4.11 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.56 - 3.50 (m, 3H), 3.45 - 3.38 (m, 1H), 3.30 - 3.27 (m, 1H), 3.24 - 3.17 (m, 1H), 3.15 - 3.09 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.72 - 2.67 (m, 1H), 2.59 - 2.38 (m, 4H), 2.33 - 2.25 (m, 1H), 2.16 - 2.10 (m, 1H), 2.04 - 1.90 (m, 10H), 1.87 - 1.65 (m, 5H).

Example S57

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-(methoxymethyl)cyclopropyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



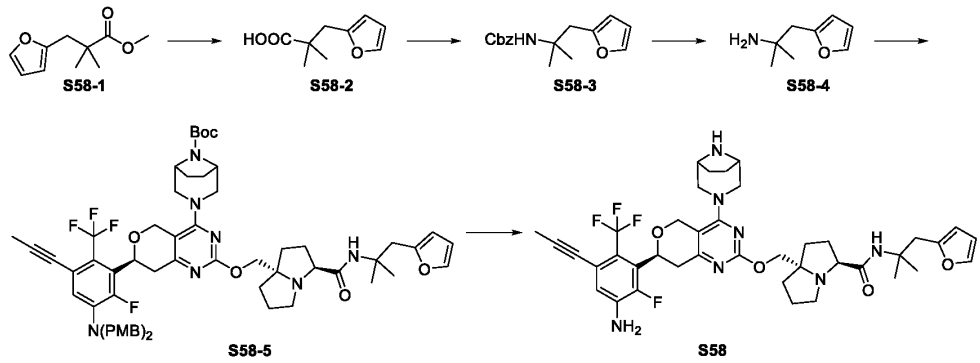
S57

Compound **S57** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1-(methoxymethyl)cyclopropyl)methanamine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 10%-34%) to afford compound **S57** (FA salt). LCMS: $[M+H]^+$ = 742.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1.2H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.26 - 4.19 (m, 2H), 4.14 (d, *J* = 12.0 Hz, 1H), 3.95 -3.80 (m, 3H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.33 (s, 3H), 3.29 - 3.15 (m, 6H), 3.10 - 3.04 (m, 1H), 2.91 - 2.82 (m, 2H), 2.19 - 2.05 (m, 4H), 2.02 (s, 3H), 2.00 - 1.76 (m, 8H), 0.56 - 0.52 (m, 2H), 0.51 - 0.45 (m, 2H).

Example S58

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-(furan-2-yl)-2-methylpropan-2-yl)hexahydro-1H-pyrrolizine-3-

carboxamide



Step 1: S58-2

To a solution of compound **S58-1** (3.6 g, 19.76 mmol) in EtOH (30 mL) and Water (15 mL) was added LiOH (2.37 g, 98.78 mmol) .The mixture was stirred at 25 °C for 12 hours. The mixture was adjusted to pH=5 with 1 N HCl, then extracted with EtOAc (50 mL), then the organic phase was concentrated to give a residue. The residue was purified by flash chromatography (PE : EtOAc = 100:1 to 0:1) to afford compound **S58-2**. LCMS: $[M-H]^-$ = 167.1.

Step 2: S58-3

To a solution of compound **S58-2** (3.32 g, 19.74 mmol) in Toluene (35 mL) was added TEA (2.00 g, 19.74 mmol, 2.75 mL) and DPPA (5.43 g, 19.74 mmol, 4.25 mL). The mixture was stirred at 60 °C for 2 hours. Then the mixture was added BnOH (4.27 g, 39.48 mmol, 4.09 mL) .The mixture was stirred at 60 °C for 10 hours. The mixture was concentrated to give a residue. The residue was purified by flash chromatography (PE : EtOAc = 100:1 to 10:1) afford compound **S58-3**. LCMS: $[M+H]^+$ = 274.0.

Step 3: S58-4

To a solution of compound **S58-3** (300 mg, 1.10 mmol) in THF (5 mL) was added Pd/C (100 mg, 10% purity). The mixture was stirred at 25 °C for 12 hours under H_2 ballon. The mixture was filtered and concentrated in vacuum to afford compound **S58-4**. LCMS: $[M+H]^+$ = 140.1.

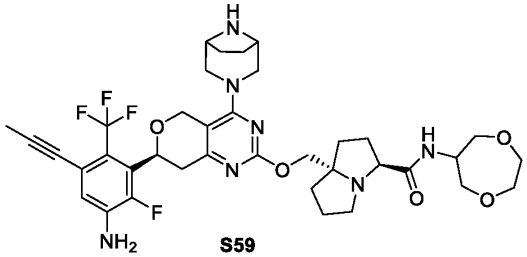
Steps 4~5: S58

Compound **S58** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S58-4**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1% FA); Gradient: (ACN): 40%-65%) to afford compound **S58** as a FA salt. LCMS: $[M+H]^+$ = 766.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.53 (brs, 1H), 7.37 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.40 - 6.25 (m, 1H), 6.13 - 6.04 (m, 1H), 5.20 - 5.12 (m, 1H), 4.81 - 4.77 (m, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.26 - 4.15

(m, 2H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.86 - 3.75 (m, 3H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.51 (d, *J* = 12.0 Hz, 1H), 3.29 - 3.20 (m, 2H), 3.14 (d, *J* = 12.0 Hz, 1H), 3.04 - 2.95 (m, 2H), 2.93 - 2.81 (m, 2H), 2.21 - 2.10 (m, 3H), 2.04 - 1.86 (m, 10H), 1.84 - 1.72 (m, 2H), 1.39 (s, 3H), 1.30 (s, 3H).

Example S59

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,4-dioxepan-6-yl)hexahydro-1H-pyrrolizine-3-carboxamide

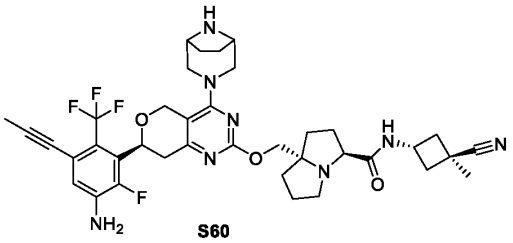


S59

Compound **S59** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 1,4-dioxepan-6-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S59**. LCMS: $[M+H]^+$ = 744.5 $[M+H]^+$。^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.22 - 5.06 (m, 1H), 4.81 - 4.78 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.29 - 4.12 (m, 3H), 4.07 (d, *J* = 12.0 Hz, 1H), 4.00 - 3.91 (m, 2H), 3.83 - 3.76 (m, 4H), 3.75 - 3.68 (m, 2H), 3.59 - 3.47 (m, 3H), 3.46 - 3.38 (m, 1H), 3.29 - 3.17 (m, 2H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.92 (m, 1H), 2.89 - 2.81 (m, 1H), 2.75 - 2.67 (m, 1H), 2.17 - 2.08 (m, 2H), 2.07 - 1.96 (m, 5H), 1.95 - 1.77 (m, 6H), 1.76 - 1.65 (m, 2H).

Example S60

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1r,3S)-3-cyano-3-methylcyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide

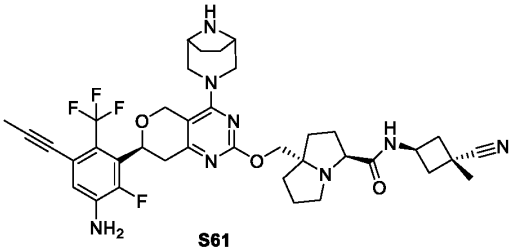


S60

Compound **S60** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **83-4** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S60**. LCMS: $[M+H]^+$= 737.5.^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.54 - 4.45 (m, 1H), 4.19 - 4.09 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.74 - 3.67 (m, 1H), 3.57 - 3.48 (m, 3H), 3.44 - 3.39 (m, 1H), 3.25 - 3.16 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.78 (m, 4H), 2.75 - 2.67 (m, 1H), 2.18 - 2.05 (m, 4H), 2.04 - 1.80 (m, 11H), 1.76 - 1.65 (m, 2H), 1.51 (s, 3H).

Example S61

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1s,3R)-3-cyano-3-methylcyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



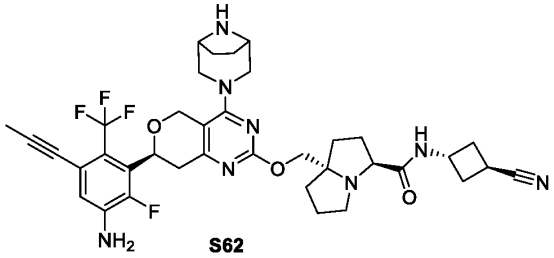
S61

Compound **S61** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **106-1** (CN 2024/119761). The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford **S61**. LCMS: $[M+H]^+$= 737.5. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.20 - 4.11 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.76 - 3.68 (m, 1H), 3.57 - 3.49 (m, 3H), 3.44 - 3.39 (m, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 16.0 Hz, 1H),

2.93 - 2.80 (m, 2H), 2.75 - 2.66 (m, 1H), 2.58 - 2.45 (m, 4H), 2.14 - 2.05 (m, 2H), 2.04 - 1.80 (m, 11H), 1.76 - 1.65 (m, 2H), 1.55 (s, 3H).

Example S62

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1r,3S)-3-cyanocyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



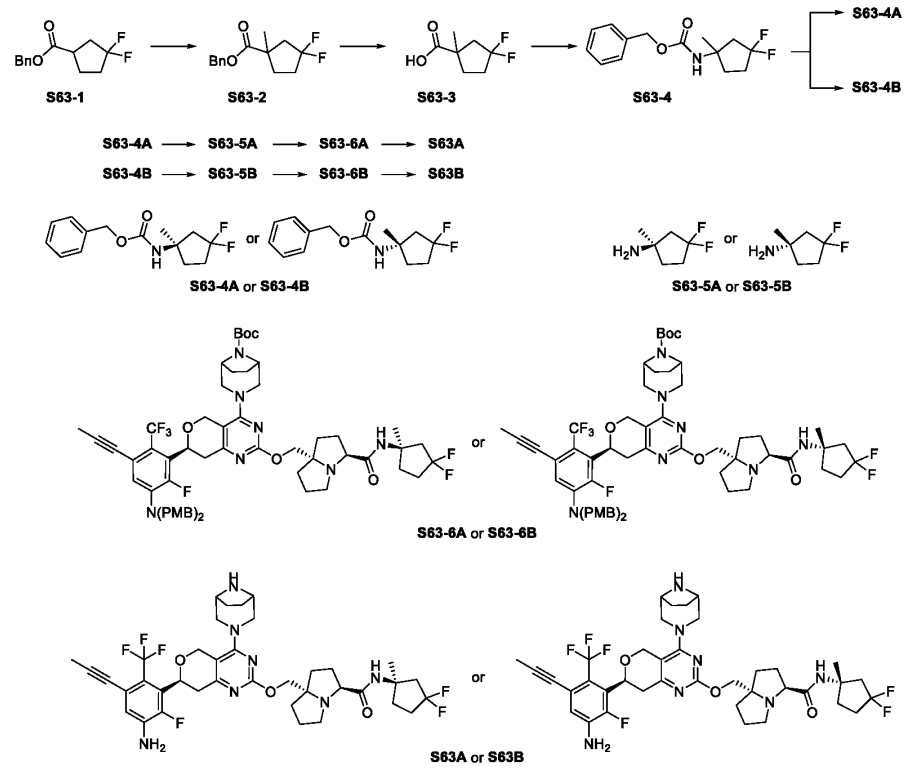
S62

Compound **S62** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with (1r,3r)-3-aminocyclobutane-1-carbonitrile. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S62**. LCMS: $[M+H]^+$ = 723.5 $[M+H]^+$。^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.23 - 5.08 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.40 - 4.27 (m, 1H), 4.21 - 4.11 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.77 - 3.69 (m, 1H), 3.65 - 3.50 (m, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.18 (m, 1H), 3.11 - 2.81 (m, 4H), 2.80 - 2.63 (m, 3H), 2.39 - 2.25 (m, 2H), 2.14 - 2.06 (m, 2H), 2.05 - 1.97 (m, 5H), 1.96 - 1.66 (m, 8H).

Example S63A and S63B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-3,3-difluoro-1-methylcyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-3,3-difluoro-1-methylcyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S63-2

To a solution of compound **S63-1** (4 g, 15.91 mmol) in dry THF (100 mL) was added LiHMDS (25 mL, 1 M in THF) dropwise at -78 °C. The mixture was stirred for 30 min. Then iodomethane (2.71 g, 19.10 mmol) was added and the reaction was stirred for 2 hours at 25 °C. The reaction was quenched with saturated solution of NH_4Cl (10 mL) at 0 °C. The resulting mixture was extracted with EA (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **S63-2**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.31 (m, 5H), 5.13 (s, 2H), 2.72 - 2.61 (m, 1H), 2.27 - 1.99 (m, 4H), 1.76 - 1.69 (m, 1H), 1.32 (s, 3H).

Step 2: S63-3

To a solution of compound **S63-2** (2.7 g, 10.11 mmol) in EtOH (50 mL) was added NaOH (50 mL, 1 M in water) dropwise at 25 °C. The reaction was stirred for 2 hours at 50 °C. The resulting mixture was adjusted to pH = 6 with HCl (1 M in water), extracted with EA (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S63-3**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.41 (s, 1H), 2.69 - 2.58 (m, 1H), 2.25 - 2.00 (m, 4H), 1.70 -

1.62 (m, 1H), 1.28 (s, 3H).

Step 3: S63-4 and S63-4A & S63-4B

To a solution of compound **S63-3** (2 g, 10.97 mmol) and DPPA (4.53 g, 16.45 mmol) in toluene (50 mL) was added TEA (4.59 mL, 32.90 mmol) at 25 °C. The resulting mixture was stirred for 2 hours at 80 °C under nitrogen atmosphere. To the above mixture was added benzyl alcohol (1.36 mL, 13.16 mmol) dropwise at 25 °C. The reaction was stirred for an additional 12 hours at 80 °C. The reaction was quenched with water (60 mL), extracted with EA (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 5:1) to afford compound **S63-4**. LCMS: $[M+H]^+$ = 270.2.

The compound **S63-4** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALCEL10, Column size: 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +(0.05%) diethylamine; Gradient: B% 10%; Wavelength: 214 nm/254nm, Flow Rate: 50 mL/ minute, Column temp: rt) to afford compound **S63-4A** and **S63-4B**. Analytical SFC method (column: DAICEL CHIRALPAK®AD-3, 3.0*100 mm, 3 μm, mobile phase A: Supercritical CO_2, mobile phase B: IPA + (0.05%) diethylamine; A/B = 95/5). Compound **S63-4A**, Rt = 1.23 min, 99.80% ee, LCMS: $[M+H]^+$ = 270.2; compound **S63-4B**, Rt = 1.60 min, 99.83% ee, LCMS: $[M+H]^+$ = 270.2.

Step 4: S63-5A

To a stirred solution of compound **S63-4A** (220 mg, 735.28 μmol) in THF (5 mL) was added Pd/C (10 mg, 10% purity) and $Pd(OH)_2/C$ (10 mg, 10% purity), the mixture was stirred at 25 °C for 12 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **S63-5A**. LCMS: $[M+H]^+$ = 136.1.

Steps 5~6：S63A

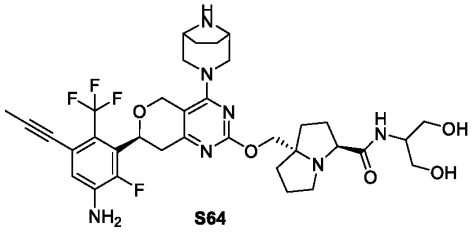
Compound **S63A** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S63-5A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30 mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-80%) to afford compound **S63A**. LCMS: $[M+H]^+$ = 762.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.74 - 3.70 (m, 1H), 3.56 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.94 - 2.90 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.81 - 2.68 (m, 2H), 2.34 - 2.05 (m, 6H), 2.04 - 1.97 (m, 4H), 1.96 - 1.80 (m, 8H), 1.75 - 1.66 (m, 2H), 1.46 (s, 3H).

Compound **S63B** was prepared analogous to compound **S63A**, replacing intermediate **S63-4A**

with intermediate **S63-4B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30 mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-80%) to afford compound **S63B**. LCMS: $[M+H]^+$ = 762.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.18 - 4.12 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.74 - 3.70 (m, 1H), 3.56 - 3.50 (m, 3H), 3.42 (d, *J* = 8.0 Hz, 1H), 3.22 (dd, *J* = 16.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.94 - 2.90 (m, 1H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.79 - 2.68 (m, 2H), 2.34 - 2.06 (m, 6H), 2.05 - 1.98 (m, 4H), 1.96 - 1.80 (m, 8H), 1.75 - 1.66 (m, 2H), 1.46 (s, 3H).

Example S64

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dihydroxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

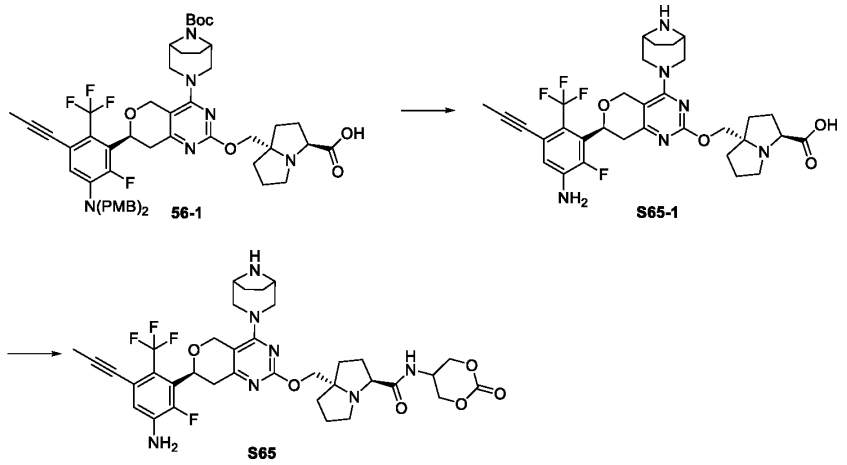


S64

Compound **S64** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride with 5-amino-1,3-dioxan-2-one. The crude product was purified was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19 mm, 5μm, ACN-H2O (0.1%NH3); Gradient: (ACN): 40%-70%) to afford compound **S64**. LCMS: $[M+H]^+$ = 718.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.80 (d, *J* = 8.0 Hz, 1H), 5.05 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 - 4.77 (m, 1H), 4.67 - 4.62 (m, 1H), 4.23 - 4.10 (m, 2H), 4.06 (d, *J* = 8.0 Hz, 1H), 4.01 - 3.92 (m, 1H), 3.85 - 3.77 (m, 1H), 3.64 (d, *J* = 4.0 Hz, 4H), 3.58 - 3.49 (m, 3H), 3.46 - 3.90 (m, 1H), 3.26 - 3.18 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.92 (m, 1H), 2.90 - 2.71 (m, 2H), 2.22 - 2.03 (m, 3H), 2.01 (s, 3H), 2.00 - 1.81 (m, 7H), 1.77 - 1.66 (m, 2H).

Example S65

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-oxo-1,3-dioxan-5-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S65-1

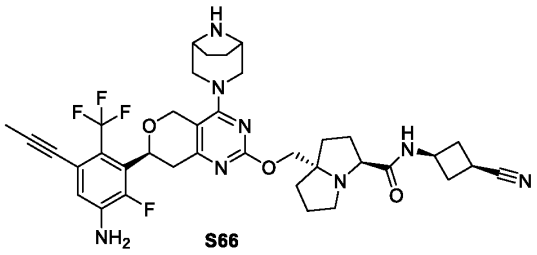
To a solution of compound **56-1** (100 mg, 101.52 μmol) (CN 2024/083328) in DCM (4.0 mL) was added TFA (1.49 g, 13.07 mmol, 1.0 mL) at room temperature. The reaction solution was stirred for 1 hour at room temperature. The resulting mixture was concentrated to afford compound **S65-1**, which was used in the next step directly without further purification. LCMS: $[M+H]^+ = 645.2$.

Step 2: S65

To a solution of compound **S65-1** (10 mg, 15.51 μmol) and 5-amino-1,3-dioxan-2-one (1.82 mg, 15.51 μmol) in THF (0.5 mL) was added DIPEA (6.0 mg, 46.53 μmol) and HATU (7.1 mg, 18.61 μmol) stirred for 2 hours at room temperature. The mixture was concentrated to give a crude product which was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19 mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 30%-70%) to afford compound **S65** as a FA salt. LCMS: $[M+H]^+ = 744.5$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.47 (s, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 5.22 - 5.15 (m, 1H), 4.83 - 4.79 (m, 1H), 4.75 - 4.64 (m, 2H), 4.47 - 4.30 (m, 2H), 4.29 - 4.22 (m, 2H), 4.19 - 4.13 (m, 1H), 4.08 - 3.95 (m, 3H), 3.77 - 3.72 (m, 1H), 3.68 - 3.56 (m, 3H), 3.27 - 3.20 (m, 2H), 3.13 - 3.01 (m, 1H), 3.00 - 2.72 (m, 2H), 2.34 - 2.10 (m, 5H), 2.09 - 2.03 (m, 3H), 2.02 (s, 3H), 1.99 - 1.79 (m, 4H).

Example S66

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1r,3S)-3-cyanocyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide



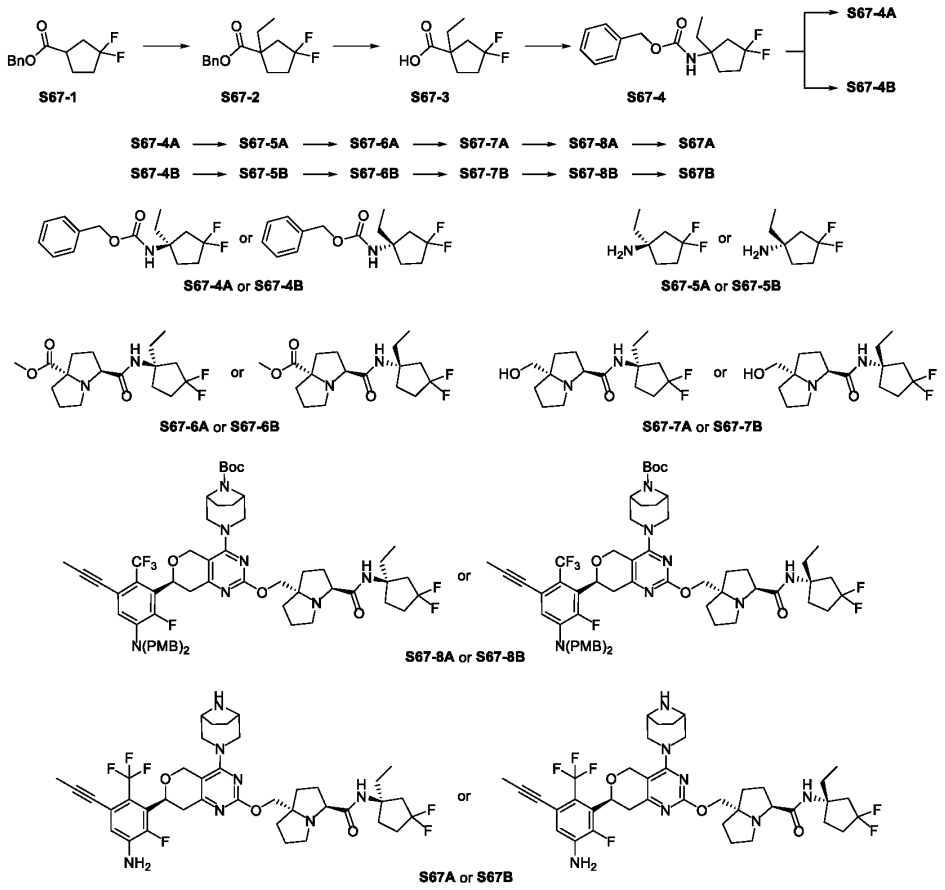
S66

Compound **S66** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with cis-3-aminocyclobutanecarbonitrile hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S66**. LCMS: $[M+H]^+$ = 723.5。^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.68 - 4.54 (m, 2H), 4.21 - 4.08 (m, 2H), 4.04 (d, *J* = 8.0 Hz, 1H), 3.76 - 3.68 (m, 1H), 3.57 - 3.48 (m, 3H), 3.45 - 3.36 (m, 1H), 3.27 - 3.17 (m, 2H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.80 (m, 2H), 2.75 - 2.61 (m, 3H), 2.51 - 2.40 (m, 2H), 2.14 - 2.04 (m, 2H), 2.02 (s, 3H), 2.00 - 1.78 (m, 8H), 1.76 - 1.64 (m, 2H).

Example S67A and S67B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-1-ethyl-3,3-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1S,5R)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-1-ethyl-3,3-difluorocyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S67-2

To a solution of compound **S67-1** (3.50 g, 14.57 mmol) in dry THF (20 mL) was added LiHMDS (21.85 mL, 1 M in THF) dropwise at -78 °C. The mixture was stirred for 30 min. Then iodoethane (2.73 g, 17.48 mmol) was added and the reaction was stirred for 2 hours at 25 °C. The reaction was quenched with saturated solution of NH_4Cl (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 100:1) to afford compound **S67-2**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.31 (m, 5H), 5.15 (s, 2H), 2.76 (q, J = 12.0 Hz, 1H), 2.43 - 2.32 (m, 1H), 2.17 - 1.99 (m, 3H), 1.78 - 1.72 (m, 3H), 0.80 (t, J = 8.0 Hz, 3H).

Step 2: S67-3

To a solution of compound **S67-2** (2 g, 7.50 mmol) in THF (100 mL) was added Pd/C (200 mg, 10% purity) and $Pd(OH)_2/C$ (200 mg, 20% purity) at 25 °C. The reaction was stirred for 2 hours at 25 °C under H_2 (1 atm) atmosphere. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure to afford crude compound **S67-3**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm

12.54 (s, 1H), 2.76 - 2.53 (m, 1H), 2.27 - 1.93 (m, 4H), 1.70 - 1.62 (m, 3H), 0.79 (t, J = 8.0 Hz, 3H).

Step 3: S67-4 and S67-4A & S67-4B

To a stirred solution of compound **S67-3** (1 g, 5.6 mmol) and DPPA (2.32 g, 8.42 mmol) in toluene (40 mL) was added TEA (2.4 mL, 16.8 mmol) at 25 °C. The resulting mixture was stirred for 2 hours at 60 °C under nitrogen atmosphere. To the above mixture was added benzyl alcohol (5.8 mL, 56 mmol) dropwise at 25 °C. The reaction was stirred for an additional 12 hours at 110 °C. The reaction was quenched with water (50 mL), extracted with EA (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 100:1) to afford compound **S67-4**. LCMS: $[M+H]^+$ = 284.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H), 7.39 - 7.28 (m, 5H), 5.01 (s, 2H), 2.68 (q, J = 12.0, 1H), 2.26 - 2.04 (m, 4H), 1.93 - 1.80 (m, 1H), 1.75 - 1.53 (m, 2H), 0.79 - 0.74 (m, 3H).

The compound **S67-4** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALPAK®IC-10, Column size: 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +(0.05%) $NH_3 \cdot H_2O$; Gradient: B% 10%; Wavelength: 214 nm/254nm, Flow Rate: 60 mL/ minute, Column temp: rt) to afford compound **S67-4A** and **S67-4B**. Analytical SFC method (column: DAICEL CHIRALPAK®AD-3, 3.0*100 mm, 3 μm, mobile phase A: Supercritical CO_2, mobile phase B: MeOH + (0.05%) diethylamine; A/B = 95/5). Compound **S67-4A**, Rt = 3.03 min, >99.00% ee, LCMS: $[M+H]^+$ = 284.2; compound **S67-4B**, Rt = 3.31 min, 97.50% ee, LCMS: $[M+H]^+$ = 284.2.

Step 4: S67-5A

To a stirred solution of compound **S67-4A** (200 mg, 705.93 μmol) in THF (10 mL) was added Pd/C (20 mg, 10% purity) and the mixture was stirred at 25 °C for 4 hours under hydrogen (15 psi) atmosphere. The reaction was filtered, the filtrate was concentrated under reduced pressure to afford compound **S67-5A**. LCMS: $[M+H]^+$ = 150.1.

Steps 5~8：S67A

Compound **S67A** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with intermediate **S67-5A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30 mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-85%) to afford compound **S67A**. LCMS: $[M+H]^+$ = 776.5. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.17 - 4.13 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.74 (dd, J = 8.0, 4.0 Hz, 1H), 3.56 - 3.50 (m, 3H), 3.42 (d, J = 8.0 Hz, 1H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.97 - 2.92 (m, 1H), 2.89 - 2.74 (m, 2H), 2.70 - 2.63 (m, 1H), 2.34 - 2.04 (m, 6H), 2.03

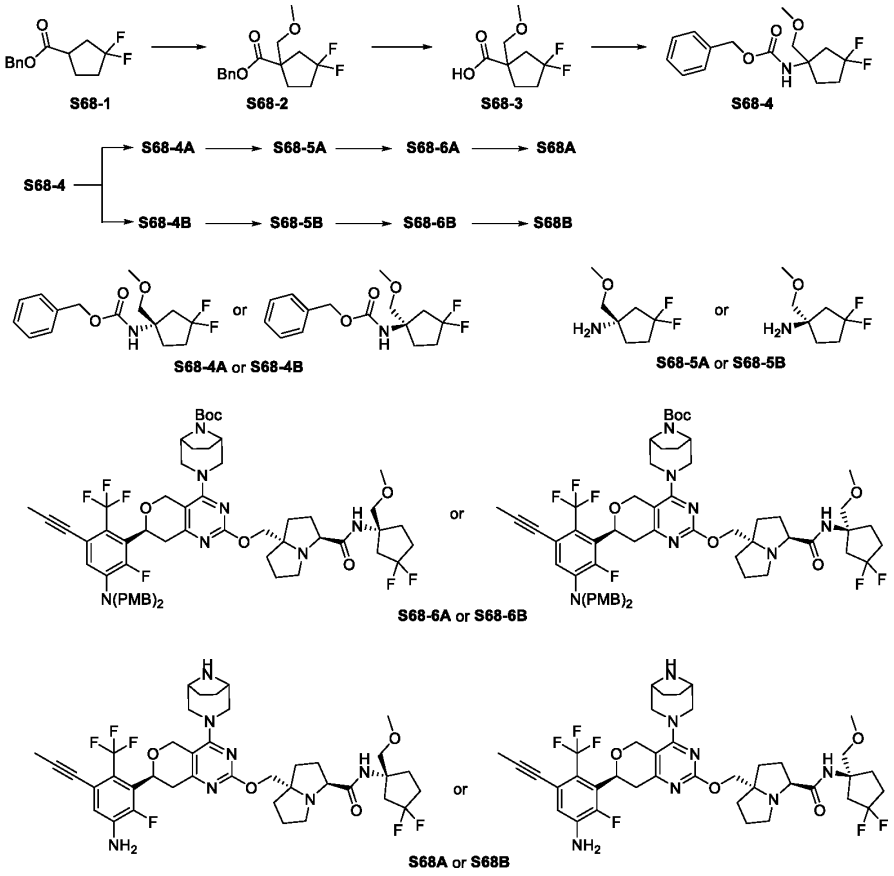
- 1.98 (m, 5H), 1.97 - 1.79 (m, 9H), 1.79 - 1.64 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H).

Compound **S67B** was prepared analogous to compound **S67A**, replacing intermediate **S67-4A** with intermediate **S67-4B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge, 250*30 mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 60%-85%) to afford compound **S67B**. LCMS: $[M+H]^+$ = 776.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.17 - 4.13 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.75 (dd, J = 8.0, 4.0 Hz, 1H), 3.56 - 3.50 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 16.0, 12.0 Hz, 1H), 3.04 (d, J = 16.0 Hz, 1H), 2.96 - 2.91 (m, 1H), 2.87 - 2.71 (m, 3H), 2.34 - 2.06 (m, 7H), 2.04 - 1.79 (m, 12H), 1.77 - 1.62 (m, 3H), 0.88 (t, J = 8.0 Hz, 3H).

Example S68A and S68B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-3,3-difluoro-1-(methoxymethyl)cyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide or

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-3,3-difluoro-1-(methoxymethyl)cyclopentyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S68-2

To a solution of compound **S68-1** (4 g, 16.65 mmol) in dry THF (60 mL) was added LiHMDS (4.18 g, 24.97 mmol) at -78 °C. The resulting mixture was stirred for 0.5 hours at -78 °C. To the above mixture was added bromo(methoxy)methane (2.50 g, 19.98 mmol) at 25 °C. The reaction was stirred for 2 hours at 25 °C. The reaction was quenched with water (50 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (PE : EtOAc = 10:1) to afford compound **S68-2**. LCMS: $[M+H]^+$ = 285.2.

Step 2: S68-3

To a solution of compound **S68-2** (2.3 g, 8.09 mmol) in EtOH (30 mL) was added 2 N NaOH (15 mL). The reaction was stirred at 25 °C for 2 hour. The mixture was concentrated under reduced pressure to afford compound **S68-3**. LCMS: $[M-H]^-$ = 193.1.

Step 3: S68-4 and S68-4A & S68-4B

To a mixture of compound **S68-3** (2 g, 10.30 mmol) in Toluene (30 mL) was added DPPA (4.25 g, 15.45 mmol) and TEA (1.56 g, 15.45 mmol). The reaction mixture was stirred at 60 °C for 3 hours. To the above mixture was added BnOH (2.23 g, 20.60 mmol) at 25 °C. The reaction was stirred for

16 hours at 60 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography, (PE : EtOAc= 10:1) to afford compound **S68-4** . LCMS: $[M+H]^+$ =300.2.

Compound **S68-4** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALPAK®IG-10, Column size: 25*250mm 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +（0.05%）DEA, A/B = 95/5,Wavelength: 214 nm/254nm, Flow Rate: 60mL/min, Column temp: RT, Injection: 1 mL, Cycle time: 5.54 min) to afford compound **S68-4A** and compound **S68-4B**. Chiral SFC analysis (chromatographic column: DAICEL CHIRALPAK®IG-3 (3.0*100mm, 3μm); Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +（0.05%） DEA, compound **S68-4A** Rt=1.701 minutes, 100.00% ee. LCMS: $[M+H]^+$ = 300.2. compound **S68-4B** Rt=2.068 minutes, 96.10% ee. LCMS: $[M+H]^+$ = 300.2.

Step 4：S68-5A

To a solution of **S68-4A** (800 mg, 2.67 mmol) in THF (10 mL) was added Pd/C (85.33 mg, 10% purity) and $Pd(OH)_2$ (112.61 mg, 10% purity) at 25 °C. The reaction was stirred overnight at 25 °C under H_2 ballon. The reaction was filtered, the filter cake was washed with MeOH (3 × 10 mL). The filtrate was concentrated under reduced pressure to afford compound **S68-5A**. LCMS: $[M+H]^+$ = 166.1.

Steps 5~6：S68A

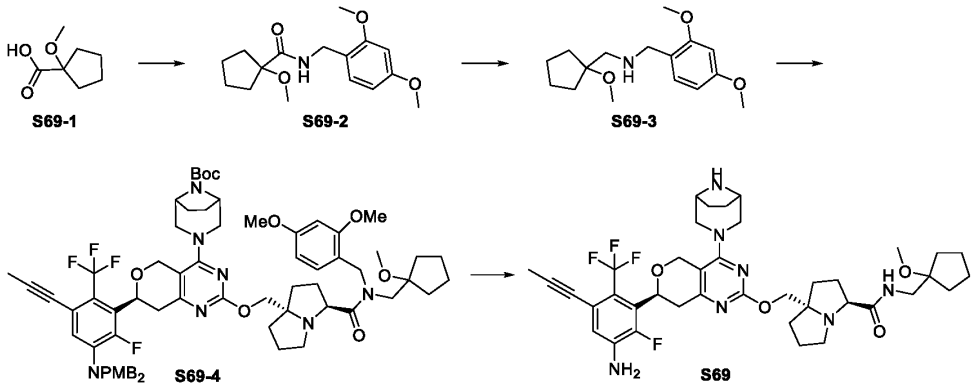
Compound **S68A** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with **S68-5A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 55%-80%) to afford compound **S68A**. LCMS: $[M+H]^+$ = 792.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.21 - 5.11 (m, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.19 - 4.11 (m, 2H), 4.06 (d, J = 8.0 Hz, 1H), 3.79 - 3.72 (m, 1H), 3.62 - 3.50 (m, 5H), 3.43 (d, J = 12.0 Hz, 1H), 3.35 (s, 3H), 3.26 - 3.17 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 3.00 - 2.94 (m, 1H), 2.89 - 2.81 (m, 1H), 2.77 - 2.69 (m, 1H), 2.67 - 2.54 (m, 1H), 2.36 - 2.23 (m, 2H), 2.19 - 2.04 (m, 5H), 2.01 (s, 3H), 2.00 - 1.77 (m,8H), 1.76 - 1.67 (m, 2H).

Compound **S68B** was prepared analogous to compound **S68A**, replacing **S68-4A** with **S68-4B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 55%-80%) to afford compound **S68B**. LCMS: $[M+H]^+$ = 792.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.21 - 5.11 (m, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.06 (d, J = 12.0

Hz, 1H), 3.78 - 3.72 (m, 1H), 3.60 (d, J = 12.0 Hz, 1H), 3.57 - 3.47 (m, 4H), 3.42 (d, J = 12.0 Hz, 1H), 3.34 (s, 3H), 3.27 - 3.17 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 3.01 - 2.94 (m, 1H), 2.89 - 2.81 (m, 1H), 2.76 - 2.68 (m, 1H), 2.66 - 2.56 (m, 1H), 2.36 - 2.22 (m, 2H), 2.17 - 2.04 (m, 5H), 2.02 (s, 3H), 2.00 - 1.77 (m, 8H), 1.76 - 1.65 (m, 2H).

Example S69

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((1-methoxycyclopentyl)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S69-2

To a solution of compound **S69-1** (500 mg, 3.47 mmol) in DMF (8 mL) was added (2,4-dimethoxyphenyl)methanamine (579.90 mg, 3.47 mmol), DIEA (896.47 mg, 6.94 mmol, 1.21 mL) and HATU (1.58 g, 4.16 mmol). The reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic phase was concentrated under vacuum. The residue was purifity by column (PE : EtOAc = 1:1) afford compound **S69-2**. LCMS: $[M+H]^+$ = 294.2.

Step 2: S69-3

To a stirred solution of compound **S69-2** (950 mg, 3.24 mmol) in THF (10 mL) was added $LiAlH_4$ (368.73 mg, 9.72 mmol). The reaction mixture was stirred at 80 °C for 48 hours. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The mixture was filtered and the combined organic phase was concentrated under vacuum. The residue was purified by column (PE : EtOAc = 0:1) afford compound **S69-3**. LCMS: $[M+H]^+$ = 280.2.

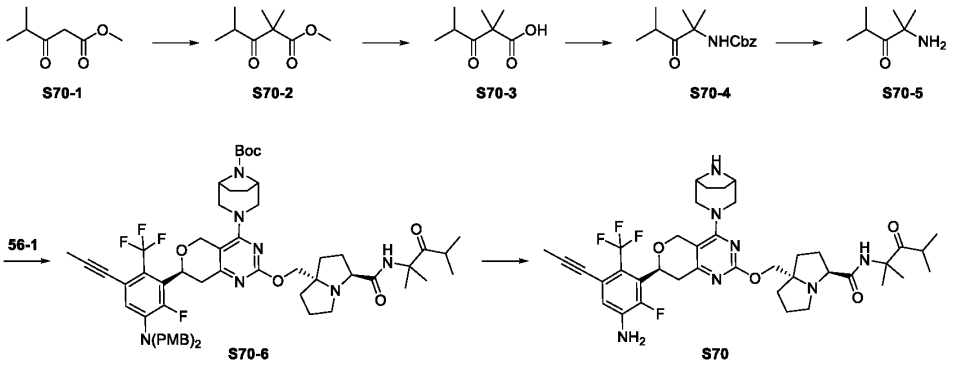
Steps 3~4: S69

Compound **S69** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S69-3**. The crude product was purified by

Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-65%) to afford compound **S69**. LCMS: $[M+H]^+$ = 756.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.81 - 4.77 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.22 - 4.10 (m, 2H), 4.07 (d, *J* = 8.0 Hz, 1H), 3.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.55 - 3.35 (m, 6H), 3.26 - 3.16 (m, 4H), 3.04 (d, *J* = 8.0 Hz, 1H), 3.00 - 2.91 (m, 1H), 2.90 - 2.79 (m, 1H), 2.78 - 2.66 (m, 1H), 2.18 - 2.08 (m, 2H), 2.06 - 1.96 (m, 5H), 1.95 - 1.60 (m, 14H), 1.58 - 1.48 (m, 2H).

Example S70

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2,4-dimethyl-3-oxopentan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S70-2

To a solution of compound **S70-1** (4 g, 27.75 mmol) in dry THF (50 mL) was added NaH (2.00 g, 83.24 mmol, 60% purity) at 0 °C. The mixture was stirred for 30 min. Then iodomethane (6.91 mL, 110.98 mmol) was added and the reaction was stirred for 3 hours at 25 °C. The reaction was quenched with saturated solution of NH_4Cl (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S70-2**. The crude product was used in the next step directly without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.73 (s, 3H), 2.90 - 2.84 (m, 1H), 1.38 (s, 6H), 1.07 (d, *J* = 4.0 Hz, 6H).

Step 2: S70-3

To a solution of the compound **S70-2** (3.3 g, 19.16 mmol) in THF (30 mL) was added $LiOH·H_2O$ (1.21 g, 28.74 mmol) at 25 °C. The reaction was stirred for 1 hour at 25 °C. The resulting mixture was concentrated under reduced pressure. The residue was diluted with water, acidified to pH = 1

with HCl (1 M in water). Then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S70-3**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.96 - 2.90 (m, 1H), 1.25 (s, 6H), 0.99 (d, J = 8.0 Hz, 6H).

Step 3: S70-4

To a stirred solution of compound **S70-3** (1 g, 6.32 mmol) and DPPA (1.43 mL, 6.64 mmol) in toluene (20 mL) was added TEA (925.12 μL, 6.64 mmol) at 25 °C. The resulting mixture was stirred for 2 hours at 60 °C under nitrogen atmosphere. To the above mixture was added benzyl alcohol (70.65 mL, 682.70 mmol) dropwise at 25 °C. The reaction was stirred for an additional 12 hours at 110 °C. The reaction was quenched with water (20 mL), extracted with EA (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **S70-4**. LCMS: $[M+H]^+$ = 264.1.

Step 4: S70-5

To a solution of compound **S70-4** (700 mg, 2.66 mmol) in MeOH (10 mL) was added Pd/C (645.7 mg, 10% purity) at 25 °C. The reaction was stirred for 2 hours at 25 °C under H_2 (1 atm) atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (5 mL × 3). The filtrate was concentrated under reduced pressure to afford crude compound **S70-5**. LCMS: $[M+H]^+$ = 130.2.

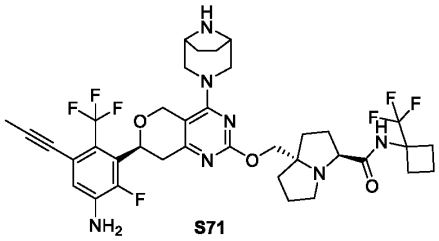
Steps 5~6: S70

Compound **S70** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S70-5**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **S70**. LCMS: $[M+H]^+$ = 756.6. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.19 - 4.13 (m, 2H), 4.06 (d, J = 12.0 Hz, 1H), 3.82 - 3.79 (m, 1H), 3.58 - 3.51 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.26 - 3.20 (m, 1H), 3.19 - 3.15 (m, 1H), 3.05 (d, J = 16.0 Hz, 1H), 2.98 - 2.93 (m, 1H), 2.85 (dd, J = 20.0, 4.0 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.12 - 2.05 (m, 2H), 2.02 (s, 3H), 2.01 - 1.81 (m, 8H), 1.76 - 1.68 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.06 (t, J = 4.0 Hz, 6H).

Example S71

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-

yl)oxy)methyl)-N-(1-(trifluoromethyl)cyclobutyl)hexahydro-1H-pyrrolizine-3-carboxamide

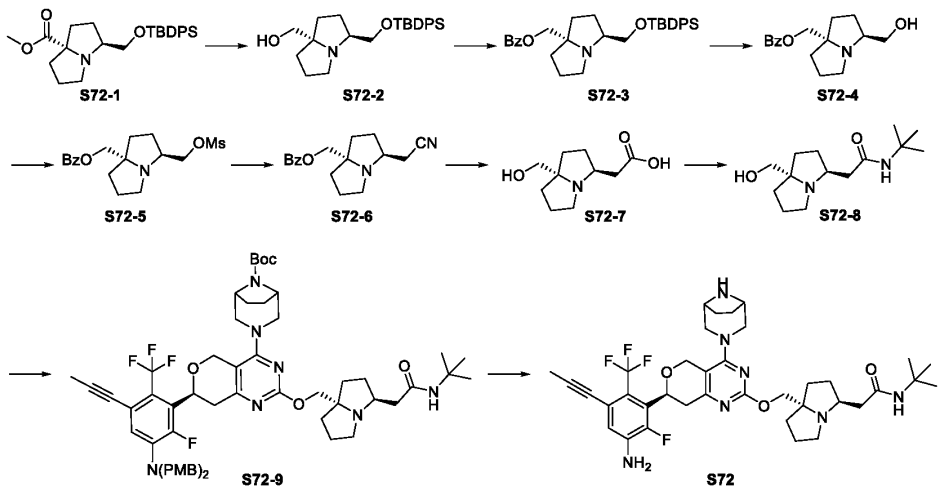


S71

Compound **S71** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 1-(trifluoromethyl)cyclobutan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*19mm, 5μm, ACN-H_2O (0.1%FA); Gradient: (ACN): 30%-55%) to afford compound **S71** (FA salt). LCMS: $[M+H]^+$ = 766.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 (s, 0.84H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.82 (d, *J* = 16.0 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.25 - 4.17 (m, 2H), 4.09 (d, *J* = 12.0 Hz, 1H), 3.91 - 3.83 (m, 3H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 16.0 Hz, 1H), 3.27 - 3.16 (m, 2H), 3.05 - 2.99 (m, 1H), 2.92 - 2.79 (m, 2H), 2.57 - 2.43 (m, 4H), 2.21 - 2.09 (m, 3H), 2.06 - 1.84 (m, 13H), 1.81 - 1.73 (m, 1H).

Example S72

2-((3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)-N-(tert-butyl)acetamide



S72-1 **S72-2** **S72-3** **S72-4**

S72-5 **S72-6** **S72-7** **S72-8**

S72-9 **S72**

Step 1: S72-2

To a stirred solution of compound **S72-1** (6 g, 13.71 mmol) in dry THF (60 mL) was added $LiAlH_4$ (8.23 mL, 20.56 mmol, 2.5 M in THF) at -60 °C. The reaction was stirred for 1 hour

at -60 °C. The reaction was warmed up to room temperature and diluted with EtOAc (20 mL), quenched with sodium sulfate decahydrate. The mixture was filtered, the filtrate was concentrated under reduced pressure to afford crude compound **S72-2**. LCMS: $[M+H]^+$ = 410.3.

Step 2: S72-3

To a stirred solution of compound **S72-2** (5.6 g, 13.67 mmol) in DCM (60 mL) was added TEA (5.72 mL, 41.01 mmol) and benzoyl chloride (3.84 g, 27.34 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 1 hour. The reaction was quenched with water (10 mL) at 0 °C, extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **S72-3**. LCMS: $[M+H]^+$ = 514.4.

Step 3: S72-4

A mixture of compound **S72-3** (7.0 g, 13.63 mmol) and HCl (100 mL, 13.63 mmol, 4.0 M in 1,4-dioxane) was stirred at 50 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was diluted with DCM, then adjusted to pH = 7 with NH_3 (7 M in MeOH). The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM:MeOH = 10:1) to afford compound **S72-4**. LCMS: $[M+H]^+$ = 276.2.

Step 4: S72-5

To a stirred solution of compound **S72-4** (1.3 g, 4.72 mmol) in DCM (15 mL) was added TEA (1.97 mL, 14.16 mmol) and methanesulfonyl chloride (1.08 g, 9.44 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at 25 °C for 16 hours. The reaction was quenched with water (15 mL) at 0 °C and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude compound **S72-5**. LCMS: $[M+H]^+$ = 354.2.

Step 5: S72-6

To a stirred solution of compound **S72-5** (1.5 g, 4.24 mmol) in DMF (20 mL) was added sodium cyanide (450.2 mg, 8.49 mmol). The reaction was stirred at 80 °C for 16 hours under nitrogen atmosphere. The reaction was cooled down to room temperature, quenched with saturated solution of $NaHCO_3$, extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 3:1) to afford compound **S72-6**. LCMS: $[M+H]^+$ = 285.2.

Step 6: S72-7

To a stirred solution of compound **S72-6** (300 mg, 1.06 mmol) in dioxane (10 mL) was added concentrated HCl (3 mL, 37% in H_2O). The reaction was stirred at 50 °C for 20 hours under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The residue was purified by reverse C18 chromatography (MeCN-H_2O (0.1% NH_3); Gradient: (MeCN): 5%-60%) to afford compound **S72-7**. LCMS: $[M+H]^+$ = 200.2.

Step 7：S72-8

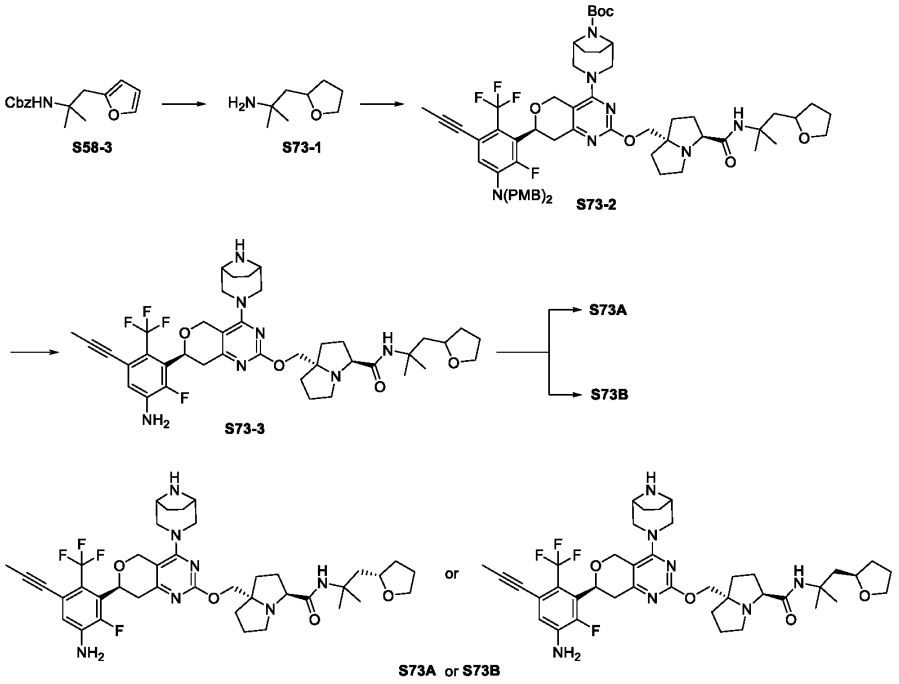
To a stirred solution of compound **S72-7** (170 mg, 853.22 μmol) in DCM (5 mL) was added 2-methylpropan-2-amine (134.49 μL, 1.28 mmol), DIPEA (445.84 μL, 2.56 mmol) and HATU (486.6 mg, 1.28 mmol) at 25 °C. The reaction was stirred at 25 °C for 16 hours. The reaction was quenched with water (10 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse C18 chromatography (MeCN-H_2O (0.1% NH_3); Gradient: (MeCN): 15%-50%) to afford compound **S72-8**. LCMS: $[M+H]^+$ = 255.2.

Steps 8~9：S72

Compound **S72** was prepared analogous to compound **16D** (CN 2024/083328), replacing intermediate **16-9D** (CN 2024/083328) with intermediate **S72-8**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **S72**. LCMS: $[M+H]^+$ = 714.5. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.20 - 4.11 (m, 2H), 3.56 - 3.50 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.99 - 2.85 (m, 2H), 2.82 - 2.72 (m, 1H), 2.58 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.44 - 2.34 (m, 1H), 2.25 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.06 - 1.99 (m, 4H), 1.98 - 1.55 (m, 11H), 1.31 (s, 9H).

Example S73A and S73B

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-methyl-1-((S)-tetrahydrofuran-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide or
(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-methyl-1-((R)-tetrahydrofuran-2-yl)propan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S73-1

To a solution of compound **S58-3** (200 mg, 0.73 mmol) in THF (5 mL) was added Pd/C (155 mg, 10% purtiy). The mixture was stirred at 25 °C under H_2 ballon for 12 hours. The mixture was filtered with a pad of celite and concentrated in vacuum to afford compound **S73-1**. LCMS: $[M+H]^+$ = 144.13.

Steps 2~4: S73A & S73B

Compound **S73-3** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with compound **S73-1**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S73-3**. LCMS: $[M+H]^+$ = 770.6.

The compound **S73-3** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALCEL10, Column size: 25*250mm, 10 μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH +(0.05%)DEA, A/B = 92.5/7.5, Wavelength: 214 nm/254nm, Flow Rate: 60mL/min) to afford compound **S73A** and **S73B**. Analytical SFC method (column: DAICEL CHIRALPAK®AD-3, 3.0*100mm, 3μm, mobile phase A: supercritical carbon dioxide, mobile phase B: IPA + (0.05%) DEA; Gradient: B%: 5%). compound **S73A**, Rt = 2.25 min, >99.90% ee value; compound **S73B**, Rt = 2.98 min, >99.90% ee value.

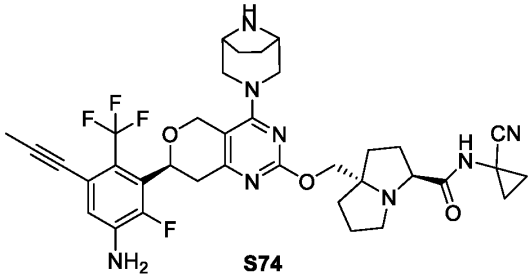
Compound **S73A**: LCMS: $[M+H]^+$ = 770.6. ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.79 - 4.76 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.22 - 4.10 (m,

2H), 4.06 (d, *J* = 12.0 Hz, 1H), 4.00 - 3.92 (m, 1H), 3.88 - 3.81 (m, 1H), 3.74 - 3.65 (m, 2H), 3.59 - 3.48 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.98 - 2.91 (m, 1H), 2.89 - 2.81 (m, 1H), 2.79 - 2.72 (m, 1H), 2.15- 2.02 (m, 4H), 2.01 (s, 3H), 1.99 - 1.87 (m, 6H), 1.86 - 1.77 (m, 4H), 1.75 - 1.66 (m, 2H), 1.51 - 1.43 (m, 1H), 1.39 (d, *J* = 6.3 Hz, 6H), 1.33 - 1.31 (m, 1H),.

Compound **S73B**: LCMS: $[M+H]^+$ = 770.6. ^{1}H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.10 (m, 1H), 4.79 - 4.76 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 4.01 - 3.94 (m, 1H), 3.86 - 3.80 (m, 1H), 3.73 - 3.66 (m, 2H), 3.59 - 3.49 (m, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 3.00 - 2.94 (m, 1H), 2.84 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.79 - 2.71 (m, 1H), 2.15 - 2.02 (m, 4H), 2.01 (s, 3H), 1.94 - 1.77 (m, 10H), 1.76 - 1.65 (m, 2H), 1.51 - 1.44 (m, 1H), 1.39 (d, *J* = 12.0 Hz, 6H), 1.34 - 1.32 (m, 1H).

Example S74

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1-cyanocyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide

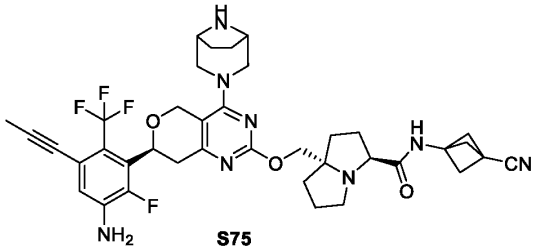


S74

Compound **S74** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 1-amino-1-cyclopropanecarbonitrile hydrochloride The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-70%) to afford compound **S74**. LCMS: $[M+H]^+$ = 709.5 $[M+H]^+$。 ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.08 (m, 1H), 4.78 - 4.73 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.21 - 4.09 (m, 2H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.75 - 3.67 (m, 1H), 3.62 - 3.49 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.93 - 2.81 (m, 2H), 2.76 - 2.67 (m, 1H), 2.16 - 2.01 (m, 6H), 2.00 - 1.79 (m, 7H), 1.78 - 1.66 (m, 2H), 1.55 - 1.46 (m, 2H), 1.27 - 1.17 (m, 2H).

Example S75

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3-cyanobicyclo[1.1.1]pentan-1-yl)hexahydro-1H-pyrrolizine-3-carboxamide

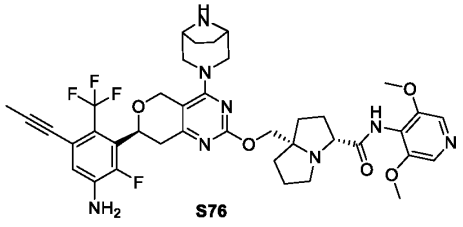


S75

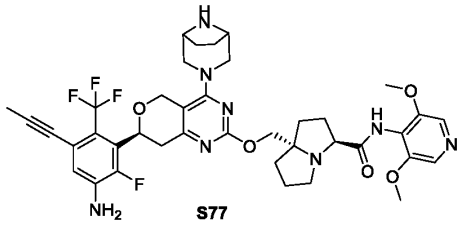
Compound **S75** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 3-aminobicyclo[1.1.1]pentane-1-carbonitrile hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S75**. LCMS: $[M+H]^+$ = 735.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.16 - 4.11 (m, 2H), 4.02 (d, *J* = 8.0 Hz, 1H), 3.68 - 3.65 (m, 1H), 3.56 - 3.49 (m, 3H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.24 - 3.17 (m, 1H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.92 - 2.80 (m, 2H), 2.73 - 2.67 (m, 1H), 2.54 (s, 6H), 2.11 - 2.03 (m, 2H), 2.01 (s, 3H), 2.00 - 1.80 (m, 8H), 1.74 - 1.64 (m, 2H).

Example S76 and S77

(3R,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3,5-dimethoxypyridin-4-yl)hexahydro-1H-pyrrolizine-3-carboxamide and (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3,5-dimethoxypyridin-4-yl)hexahydro-1H-pyrrolizine-3-carboxamide



S76



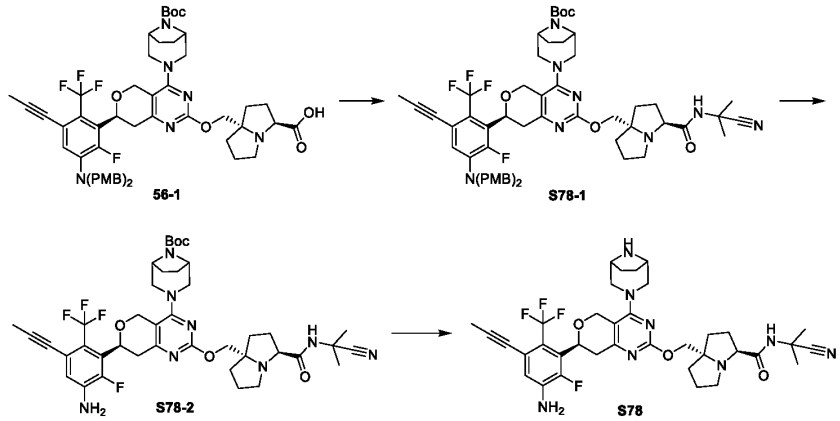
S77

Compound **S76** and **S77** were prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 3,5-dimethoxypyridin-4-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-

H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S76** and **S77**. Compound **S76**. LCMS: $[M+H]^+$ = 781.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.03 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.07 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 6H), 3.55 - 3.34 (m, 5H), 3.26 - 3.21 (m, 1H), 3.15 - 3.09 (m, 1H), 2.96 (d, *J* = 16.0 Hz, 1H), 2.84 - 2.68 (m, 2H), 2.38 - 2.29 (m, 1H), 2.21 - 2.08 (m, 2H), 2.04 - 1.91 (m, 7H), 1.87 - 1.72 (m, 4H), 1.69 - 1.59 (m, 1H). Compound **S77**. LCMS: $[M+H]^+$ = 781.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.06 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 - 4.77 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.18 - 4.12 (m, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 4.07 - 4.00 (m, 1H), 3.94 (s, 6H), 3.61 - 3.50 (m, 3H), 3.47 - 3.40 (m, 1H), 3.26 - 3.19 (m, 1H), 3.13 - 3.03 (m, 2H), 2.94 - 2.82 (m, 2H), 2.25 - 2.08 (m, 3H), 2.08 - 1.88 (m, 8H), 1.87 - 1.67 (m, 4H).

Example S78

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(2-cyanopropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S78-1

To a solution of compound **56-1** (200 mg, 0.20 mmol) (CN 2024/083328) in ACN (3 mL) was added 2-amino-2-cyanopropane (19 mg, 0.22 mmol), TCFH (114 mg, 0.40 mmol) and NMI (50 mg, 0.61 mmol) at 25 °C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM : MeOH = 20:1) to afford compound **S78-1**. LCMS: $[M+H]^+$ = 1051.6.

Step 2: S78-2

To a solution of compound **S78-1** (100 mg, 0.10 mmol) in DCM (1 mL) was added DDQ (47.51 mg, 0.21 mmol) at 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture

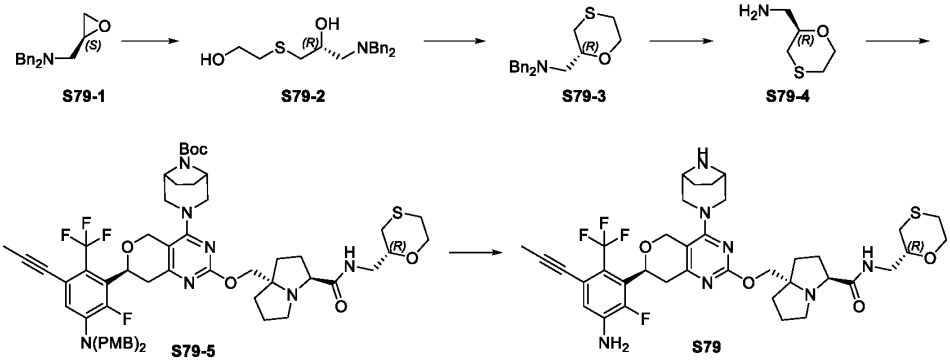
was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM : MeOH = 20:1) to afford compound **S78-2**. LCMS: $[M+H]^+$ = 811.6.

Step 3: S78

To a solution of compound **S78-2** (200 mg, 0.25 mmol) in DCM (1 mL) was added lutidine (53 mg, 0.49 m mol) and TMSOTf (220 mg, 0.99 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hours. The reaction mixture was concentrated under reduced pressure. The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-70%) to afford compound **S78**. LCMS: $[M+H]^+$ = 711.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.11 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.19 - 4.12 (m, 2H), 4.05 (d, *J* = 12.0 Hz, 1H), 3.79 - 3.73 (m, 1H), 3.60 - 3.51 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.26 - 3.17 (m, 1H), 3.05 (d, *J* = 12.0 Hz, 1H), 2.94 - 2.89 (m, 1H), 2.88 - 2.81 (m, 1H), 2.80 - 2.73 (m, 1H), 2.20 - 2.03 (m, 3H), 2.02 (s, 3H), 2.00 - 1.91 (m, 4H), 1.90 - 1.80 (m, 3H), 1.78 - 1.69 (m, 2H), 1.67 (s, 6H).

Example S79

(3S,7aS)-N-(((R)-1,4-oxathian-2-yl)methyl)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S79-2

To a solution of compound **S79-1** (1 g, 3.95 mmol) in toluene (10 mL) was added 2-sulfanylethanol (308.41 mg, 3.95 mmol, 276.85 μL) and TEA (798.85 mg, 7.89 mmol, 1.10 mL) at 25 °C. The reaction mixture was stirred at 100 °C for 12 hours. The residue was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S79-2**. LCMS: $[M+H]^+$ = 332.2.

Step 2: S79-3

To a solution of compound **S79-2** (750 mg, 2.26 mmol) was added t-BuOK (507.79 mg, 4.53 mmol) at 0 °C. Then 4-methylbenzenesulfonyl chloride (431.37 mg, 2.26 mmol) in THF (1.5 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (PE : EtOAc = 1:1) to afford compound **S79-3**. LCMS: $[M+H]^+ = 314.2$.

Step 3: S79-4

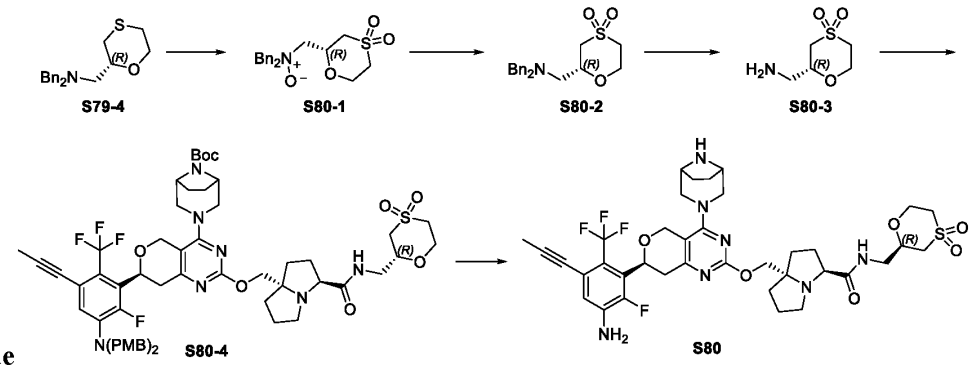
To a solution of compound **S79-3** (20 mg, 63.80 μmol) in DCM (1.0 mL) was added DDQ (57.94 mg, 255.22 μmol) at 25 °C. The reaction mixture was stirred at 25 °C for 4 hours. The reaction was quenched with 1 N HCl (10 mL), and the mixture was extracted with EtOAc (3 × 15 mL). The aqueous layer was concentrated under reduced pressure to afford compound **S79-4**. LCMS: $[M+H]^+ = 134.2$.

Steps 4~5: S79

Compound **S79** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S79-4**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S79**. LCMS: $[M+H]^+ = 760.5$. ^1H NMR (400 MHz, CD_3DO) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.23 - 4.12 (m, 3H), 4.06 (d, J = 8.0 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.75 - 3.63 (m, 2H), 3.61 - 3.51 (m, 3H), 3.45 - 3.37 (m, 1H), 3.29 - 3.25 (m, 2H), 3.23 - 3.16 (m, 1H), 3.06 (d, J = 12.0 Hz, 1H), 2.97 - 2.70 (m, 4H), 2.64 - 2.55 (m, 1H), 2.42 - 2.34 (m, 1H), 2.31 - 2.23 (m, 1H), 2.16 - 2.08 (m, 2H), 2.07 - 2.01 (m, 4H), 2.00 - 1.80 (m, 7H), 1.78 - 1.67 (m, 2H).

Example S80

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(((R)-4,4-dioxido-1,4-oxathian-2-yl)methyl)hexahydro-1H-pyrrolizine-3-



carboxamide

Step 1: S80-1

To a solution of compound **S79-4** (30 mg, 95.71 μmol) in DCM (2.0 mL) was added m-CPBA (66.06 mg, 382.83 μmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. The residue was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S80-1**. LCMS: $[M+H]^+ = 362.2$.

Step 2: S80-2

To a solution of compound **S80-1** (120 mg, 331.99 μmol) in ACN (2 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (84.31 mg, 331.99 μmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. The residue was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S80-2**. LCMS: $[M+H]^+ = 346.2$.

Step 3: S80-3

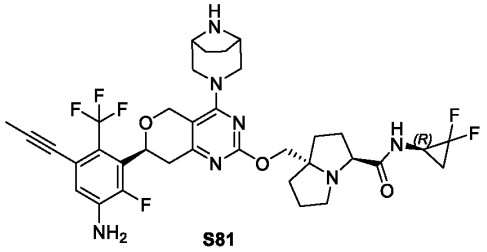
To a solution of **S80-2** (70 mg, 202.63 μmol) in MeOH (2.0 mL) was added Pd/C (21.56 mg,10% purity) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hours under H_2 ballon. The reaction was filtered, the filter cake was washed with MeOH (3 × 2 mL). The filtrate was concentrated under reduced pressure to afford compound **S80-3**. LCMS: $[M+H]^+ = 166.2$.

Steps 4~5: S80

Compound **S80** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with intermediate **S80-3**. The residue was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford Compound **S80**. LCMS: $[M+H]^+ = 792.5$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.20 - 5.10 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.36 - 4.29 (m, 1H), 4.20 - 4.10 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 4.01 - 3.89 (m, 2H), 3.81 - 3.75 (m, 1H), 3.55 - 3.49 (m, 3H), 3.48 - 3.33 (m, 3H), 3.29 - 3.19 (m, 2H), 3.18 - 3.13 (m, 1H), 3.10 - 3.00 (m, 3H), 2.92 - 2.82 (m, 2H), 2.79 - 2.69 (m, 1H), 2.16 - 2.06 (m, 2H), 2.02 (s, 3H), 2.00 - 1.79 (m, 8H), 1.76 - 1.64 (m, 2H).

Example S81

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((R)-2,2-difluorocyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide

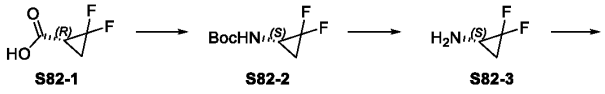


S81

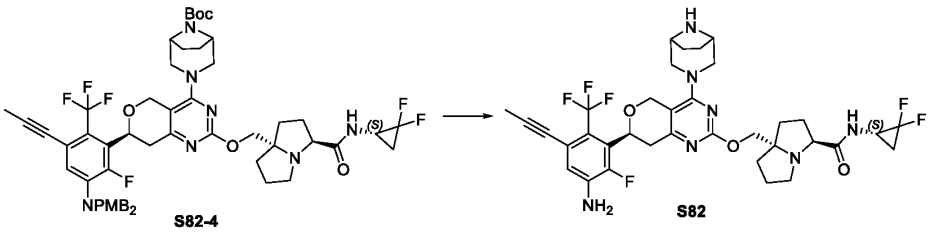
Compound **S81** was prepared analogous to compound **56** (CN 2024/083328), replacing (S)-3,3-difluorocyclopentanamine hydrochloride (1R)-2,2-difluorocyclopropan-1-amine hydrochloride. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **S81**. LCMS: $[M+H]^+$ = 720.4. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.80 - 4.76 (m, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.04 (d, J = 12 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.657 - 3.49 (m, 3H), 3.45 - 3.38 (m, 1H), 3.36 - 3.32 (m, 1H), 3.25 - 3.16 (m, 1H), 3.07 - 3.00 (m, 1H), 2.94 - 2.80 (m, 2H), 2.78 - 2.69 (m, 1H), 2.16 - 2.03 (m, 3H), 2.01 (s, 3H), 2.00 - 1.97 (m, 1H), 1.96 - 1.91 (m, 3H), 1.90 - 1.78 (m, 4H), 1.77 - 1.65 (m, 2H), 1.49 - 1.39 (m, 1H).

Example S82

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-((S)-2,2-difluorocyclopropyl)hexahydro-1H-pyrrolizine-3-carboxamide



S82-1 S82-2 S82-3



S82-4 S82

Step 1: S82-2

To a solution of compound **S82-1** (500 mg, 4.10 mmol) in 2-methylpropan-2-ol (10 mL) was added TEA (621.71 mg, 6.14 mmol) and DPPA (1.69 g, 6.14 mmol) at 25 °C. The reaction mixture was stirred at 90 °C for 16 hours. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 45 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (PE : EtOAc = 3:1) to afford compound **S82-2**. LCMS: $[M+H-56]^+ = 138.4$.

Step 2: S82-3

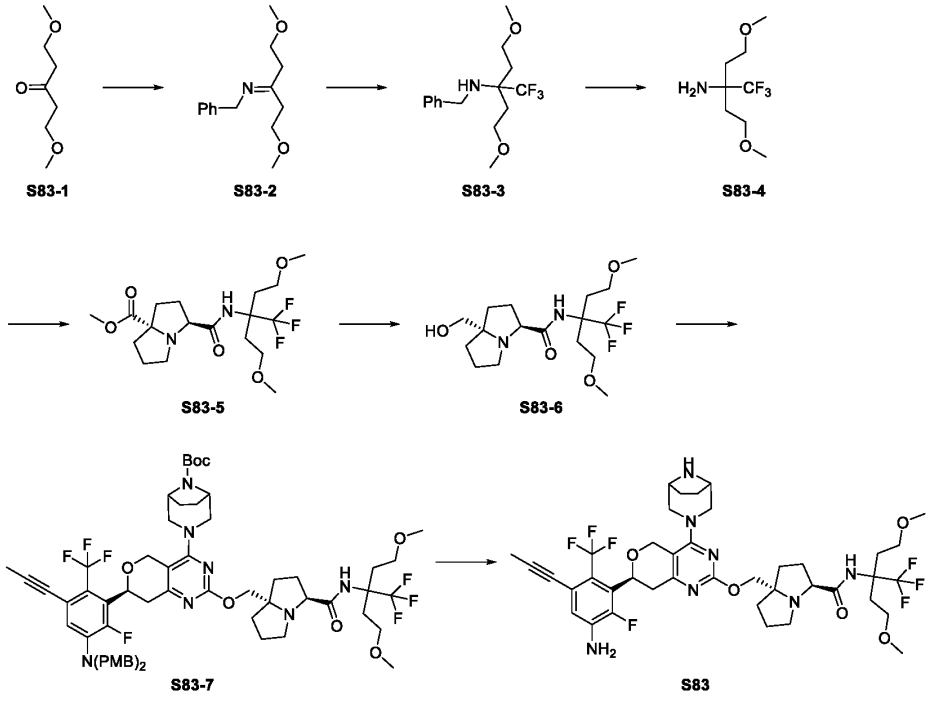
A solution of compound **S82-2** (300 mg, 1.55 mmol) in HCl (3 mL, 4.0 M in 1,4-dioxane) was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum to give compound **S82-3**. LCMS: $[M+H]^+ = 93.9$.

Steps 3~4: S82

Compound **S82** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with compound **S82-3**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-85%) to afford compound **S82**. LCMS: $[M+H]^+ = 720.4$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.05 (d, J = 12.0 Hz, 1H), 3.82 - 3.71 (m, 1H), 3.58 - 3.49 (m, 3H), 3.42 (d, J = 12.0 Hz, 1H), 3.36 - 3.32 (m, 1H), 3.26 - 3.17 (m, 1H), 3.04 (d, J = 16.0 Hz, 1H), 2.94 - 2.80 (m, 2H), 2.78 - 2.70 (m, 1H), 2.20 - 2.03 (m, 3H), 2.01 (s, 3H), 2.00 - 1.79 (m, 8H), 1.77 - 1.65 (m, 2H), 1.49 - 1.38 (m, 1H).

Example S83

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,5-dimethoxy-3-(trifluoromethyl)pentan-3-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S83-2

To a solution of compound **S83-1** (500 mg, 3.4 mmol) in DCM (5 mL) was added phenylmethanamine (350 mg, 3.3 mmol) and $MgSO_4$ (823 mg, 6.8 mmol) at 25 °C. The reaction mixture was stirred at 25°C for 48 hours. The suspension was filtered through a pad of Celite. The combined filtrates were concentrated to afford compound **S83-2**. LCMS: $[M+H]^+$ = 236.2.

Step 2: S83-3

To a solution of compound **S83-2** (800 mg, 3.4 mmol) in ACN (10 mL) was added DMF (750 mg, 10.2 mmol), KHF_2 (200 mg, 2.5 mmol), TFA (775 mg, 6.8 mmol), trimethyl(trifluoromethyl)silane (965 mg, 6.8 mmol) at 0 °C. The mixture was stirred at 25 °C for 4 hours. The mixture was adjusted to pH = 8-9 with sat Na_2CO_3. The resulting solution was extracted with EtOAc (3 x 50 mL). The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography (PE : EtOAc = 5:1) to afford compound **S83-3**. LCMS: $[M+H]^+$ = 306.1.

Step 3: S83-4

To a solution of compound **S83-3** (120 mg, 0.39 mmol) in THF (5 mL) was added was added Pd/C (20 mg, 10% purtiy) and $Pd(OH)_2/C$ (20 mg, 10% purtiy). The mixture was stirred at 50 °C for 16 hours under H_2 ballon, The suspension was filtered through a pad of Celite and the filter was washed with EtOAc (20mL×3). HCl (4M in EA) The mixture was added to adjusted to pH = 3-4 with HCl (4M in EtOAc). The combined filtrates were concentrated to dryness to afford compound **S83-**

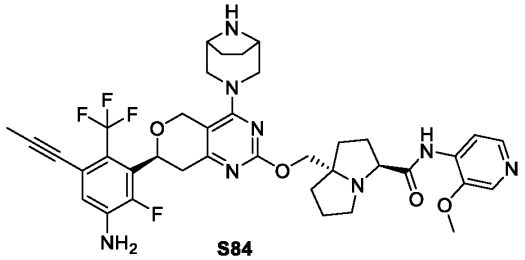
4. LCMS: $[M+H]^+ = 216.2$.

Steps 4~7: S83

Compound **S83** was prepared analogous to compound **2**, replacing 1-methylcyclopropylamine hydrochloride with compound **S83-4**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 40%-70%) to afford compound **S83**. LCMS: $[M+H]^+ = 842.6$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.18 - 5.09 (m, 1H), 4.77 - 4.73 (m, 1H), 4.67 - 4.63 (m, 1H), 4.20 - 4.05 (m, 3H), 3.80 - 3.76 (m, 1H), 3.61 - 3.47 (m, 7H), 3.45 - 3.39 (m, 1H), 3.32 (s, 6H), 3.26 - 3.14 (m, 2H), 3.08 - 2.97 (m, 2H), 2.88 - 2.80 (m, 1H), 2.73 - 2.64 (m, 1H), 2.60 - 2.51 (m, 1H), 2.42 - 2.34 (m, 1H), 2.29 - 2.17 (m, 2H), 2.17 - 2.04 (m, 2H), 2.01 (s, 3H), 2.00 - 1.80 (m, 7H), 1.76 - 1.65 (m, 2H).

Example S84

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3-methoxypyridin-4-yl)hexahydro-1H-pyrrolizine-3-carboxamide



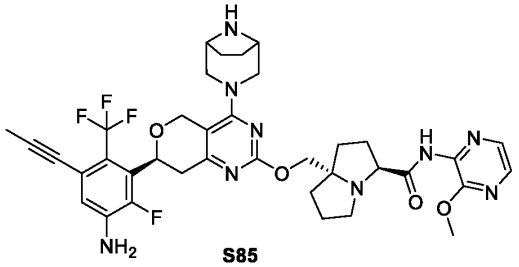
S84

Compound **S84** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 3-methoxypyridin-4-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-60%) to afford compound **S84**. LCMS: $[M+H]^+ = 751.5$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.32 (d, J = 4.0 Hz, 1H), 8.24 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 4.14 - 4.07 (m, 2H), 4.01 (s, 3H), 3.77 - 3.73 (m, 2H), 3.63 (d, J = 12.0 Hz, 1H), 3.51 (d, J = 16.0 Hz, 1H), 3.26 - 3.21 (m, 1H), 3.13 (d, J = 12.0 Hz, 1H), 3.01 - 2.95 (m, 1H), 2.87 (dd, J = 16.0, 4.0 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.26 - 2.07 (m, 4H), 2.02 (s, 3H), 1.99 - 1.89 (m, 6H), 1.83 - 1.73 (m, 2H).

Example S85

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-

((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3-methoxypyrazin-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

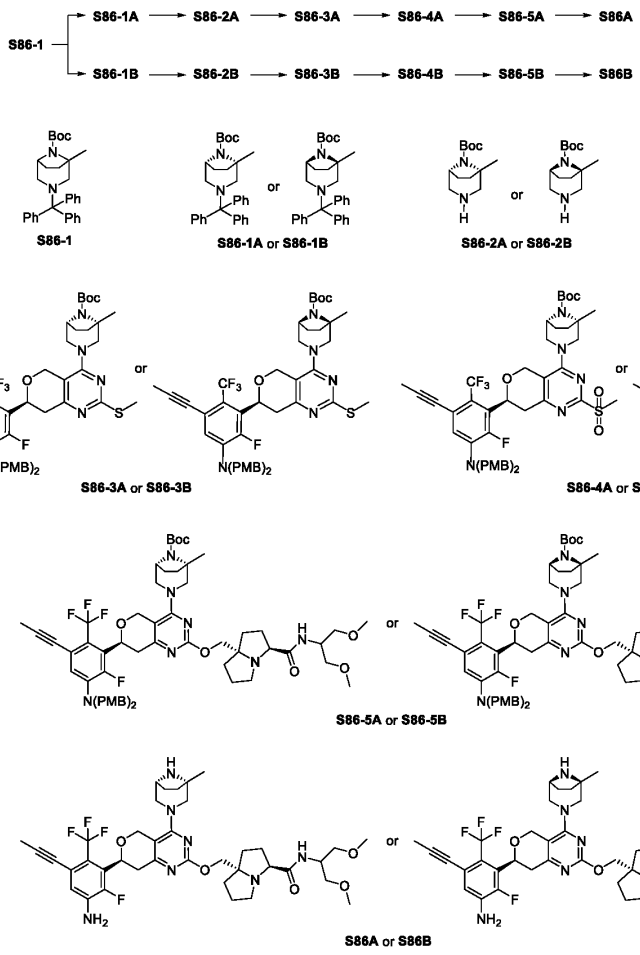


S85

Compound **S85** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 3-methoxypyrazin-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Xbridge-C18, 250*30mm, 5μm, ACN-H_2O (0.1%NH_3); Gradient: (ACN): 30%-60%) to afford compound **S85**. LCMS: $[M+H]^+$ = 752.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.94 (d, *J* = 4.0 Hz, 1H), 7.90 (d, *J* = 4.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 4.08 - 4.05 (m, 1H), 4.03 (s, 3H), 3.59 - 3.53 (m, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.23 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.08 - 3.02 (m, 2H), 2.89 - 2.81 (m, 2H), 2.26 - 2.19 (m, 1H), 2.17 - 2.10 (m, 2H), 2.02 (s, 3H), 1.99 - 1.89 (m, 5H), 1.85 - 1.70 (m, 4H).

Example S86A and **S86B**

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1S,5R)-1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide or (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S86-1A & S86-1B

The compound **S86-1** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALCEL10, Column size: 25*250mm, 10μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH + (0.05%) DEA; A/B = 92.5/7.5; Wavelength: 214 nm/254nm, Flow Rate: 60 mL/minute, Column temp: rt; Cycle time: 10 min) to afford compound **S86-1A** and **S86-1B**. Analytical SFC method (column: DAICEL CHIRALPAK®AD-3, 3.0*100 mm, 3 μm, mobile phase A: Supercritical CO_2, mobile phase B: IPA + (0.05%) DEA; A/B = 95/5). Compound **S86-1A**, Rt = 3.36 min, 99.67% ee, LCMS: $[M+H]^+$ = 469.2; compound **S86-1B**, Rt = 3.74 min, 99.10% ee, LCMS: $[M+H]^+$ = 469.2.

Step 2: S86-2A

To a solution of **S86-1A** (400 mg, 853.55 μmol) in THF (15 mL) was added HCl (2.56 mL, 1 M in water). The reaction was stirred at 25 °C for 4 hours. The reaction was adjusted with saturated solution of $NaHCO_3$ to pH = 7, extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate

was concentrated under reduced pressure to afford crude compound **S86-2A**. LCMS: $[M+H]^+$ = 227.1.

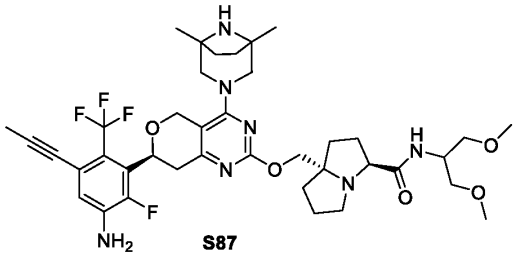
Steps 3~6：S86A

Compound **S86A** was prepared analogous to compound **53** (CN 2024/083328), replacing intermediate **53-4** with intermediate **S86-2A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **S86A**. LCMS: $[M+H]^+$ = 760.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.82 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.23 - 4.17 (m, 2H), 4.11 (d, *J* = 12.0 Hz, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.81 - 3.78 (m, 1H), 3.59 (d, *J* = 8.0 Hz, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.49 - 3.43 (m, 4H), 3.40 (d, *J* = 16.0 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.26 - 3.18 (m, 1H), 2.99 - 2.95 (m, 1H), 2.88 - 2.83 (m, 2H), 2.79 - 2.72 (m, 1H), 2.14 - 2.06 (m, 3H), 2.02 (s, 3H), 1.99 - 1.82 (m, 6H), 1.77 - 1.66 (m, 2H), 1.57 - 1.50 (m, 1H), 1.32 (s, 3H).

Compound **S86B** was prepared analogous to compound **S86A**, replacing intermediate **S86-1A** with intermediate **S86-1B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-80%) to afford compound **S86B**. LCMS: $[M+H]^+$ = 759.9. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.23 - 4.10 (m, 3H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.78 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.55 (d, *J* = 4.0 Hz, 1H), 3.50 - 3.41 (m, 5H), 3.34 (s, 3H), 3.33 (s, 3H), 3.26 - 3.15 (m, 2H), 3.01 - 2.92 (m, 2H), 2.85 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.16 - 2.06 (m, 2H), 2.02 (s, 3H), 2.01 - 1.80 (m, 7H), 1.77 - 1.68 (m, 2H), 1.52 - 1.44 (m, 1H), 1.29 (s, 3H).

Example S87

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-1,5-dimethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



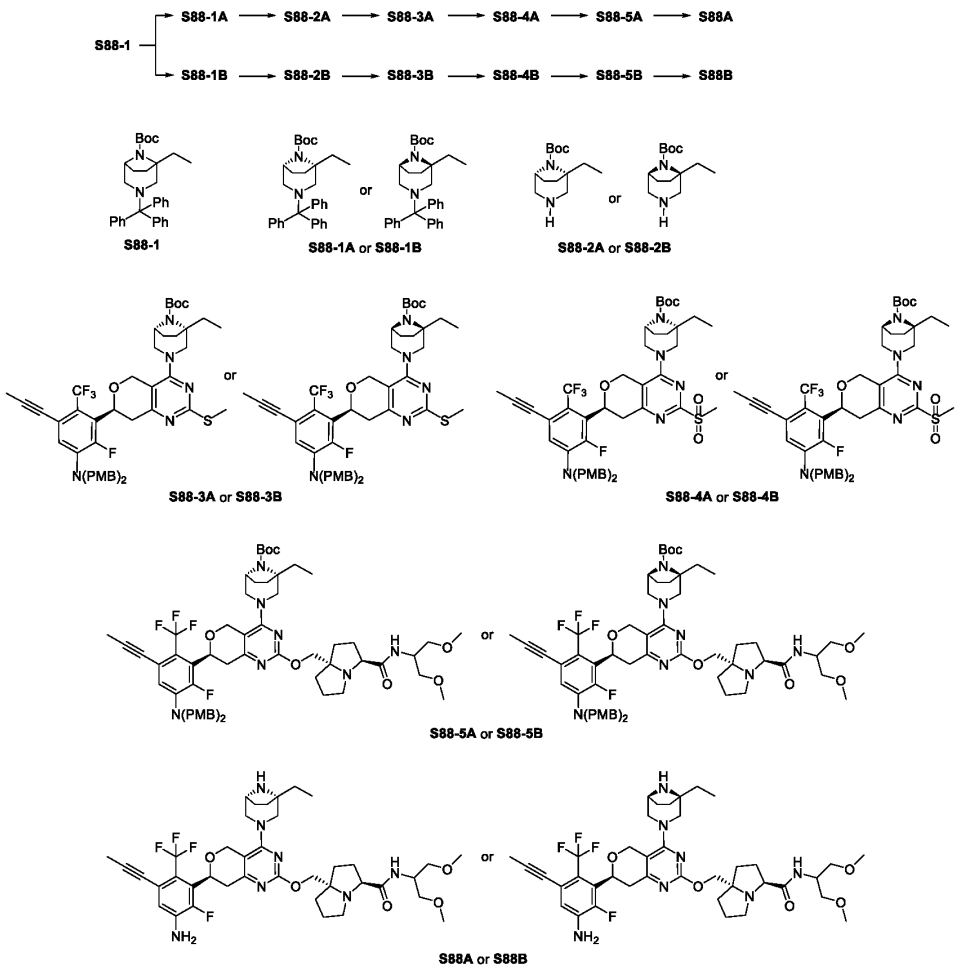
S87

Compound **S87** was prepared analogous to compound **S86A**, replacing intermediate **S86-2A**

with 1,1-dimethylethyl 1,5-dimethyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-80%) to afford compound **S87**. LCMS: $[M+H]^+$ = 774.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.17 (dd, J = 12.0, 4.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.22 - 4.16 (m, 2H), 4.10 - 4.04 (m, 2H), 3.77 (dd, J = 8.0, 4.0 Hz, 1H), 3.49 - 3.40 (m, 5H), 3.34 (s, 3H), 3.33 (s, 3H), 3.21 (dd, J = 20.0, 12.0 Hz, 1H), 3.13 (d, J = 12.0 Hz, 1H), 2.98 - 2.93 (m, 1H), 2.85 (dd, J = 16.0, 4.0 Hz, 1H), 2.77 - 2.71 (m, 2H), 2.15 - 2.09 (m, 3H), 2.01 (s, 3H), 1.99 - 1.81 (m, 5H), 1.76 - 1.70 (m, 2H), 1.66 - 1.55 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H).

Example S88A and **S88B**

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1S,5R)-1-ethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide or (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-1-ethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1: S88-1A & S88-1B

The compound **S88-1** was separated by preparative SFC (System: Waters SFC 150, Column name: DAICEL CHIRALPAK®AS-10, Column size: 25*250mm, 10μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH + (0.05%) NH_3·MeOH; A/B = 70/30; Wavelength: 214 nm/254nm, Flow Rate: 60 mL/minute, Column temp: rt; Cycle time: 12 min) to afford compound **S88-1A** and **S88-1B**. Analytical SFC method (column: DAICEL CHIRALPAK®AS-10, 25*250 mm, 10 μm, mobile phase A: Supercritical CO_2, mobile phase B: MeOH + (0.05%) NH_3·MeOH; A/B = 70/30). Compound **S88-1A**, Rt = 3.321 min, >99.00% ee, LCMS: $[M+H]^+$ = 483.2; compound **S88-1B**, Rt = 5.229 min, 98.10% ee, LCMS: $[M+H]^+$ = 483.2.

Step 2: S88-2A

To a solution of **S88-1A** (200 mg, 414.37 μmol) in THF (3 mL) was added HCl (1.24 mL, 1 M in water). The reaction was stirred at 25 °C for 0.5 hours. The reaction was adjusted with saturated solution of $NaHCO_3$ to pH = 7, extracted with EtOAc (20 mL × 3). The combined organic

layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S88-2A**. LCMS: $[M+H]^+ = 241.2$.

Steps 3~6：S88A

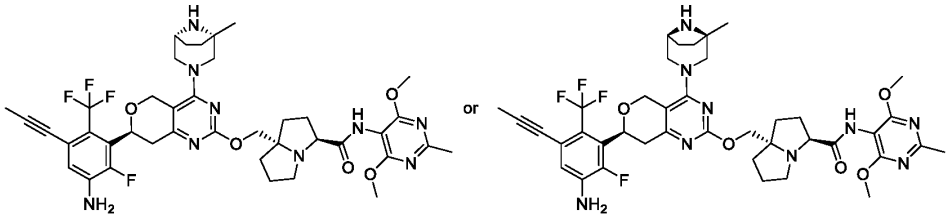
Compound **S88A** was prepared analogous to compound **S86A**, replacing intermediate **S86-2A** with intermediate **S88-2A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5 μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 30%-80%) to afford compound **S88A**. LCMS: $[M+H]^+ = 774.6$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 12.0, 4.0 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.23 - 4.15 (m, 2H), 4.11 (d, J = 16.0 Hz, 1H), 4.07 (d, J = 12.0 Hz, 1H), 3.79 - 3.76 (m, 1H), 3.57 - 3.52 (m, 2H) , 3.49 - 3.43 (m, 4H), 3.34 (s, 3H), 3.33 (s, 3H), 3.26 - 3.14 (m, 2H), 3.01 (d, J = 12.0 Hz, 1H), 2.98 - 2.93 (m, 1H) , 2.86 (dd, J = 16.0, 4.0 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.15 - 2.06 (m, 2H), 2.02 (s, 3H), 2.00 - 1.81 (m, 7H), 1.76 - 1.60 (m, 4H), 1.55 - 1.47 (m, 1H) , 1.01 (t, J = 8.0 Hz, 3H).

Compound **S88B** was prepared analogous to compound **S88A**, replacing intermediate **S88-1A** with intermediate **S88-1B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **S88B**. LCMS: $[M+H]^+ = 774.6$. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 12.0 Hz, 1H), 4.22 - 4.17 (m, 2H), 4.07 (d, J = 8.0 Hz, 1H), 3.81 - 3.77 (m, 1H), 3.58 - 3.50 (m, 2H), 3.49 - 3.44 (m, 4H), 3.43 - 3.39 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.25 - 3.17 (m, 1H), 2.99 - 2.93 (m, 1H), 2.86 (dd, J = 16.0, 4.0 Hz, 1H), 2.81 - 2.70 (m, 2H), 2.17 - 2.03 (m, 3H), 2.02 (s, 3H), 1.99 - 1.84 (m, 6H), 1.77 - 1.60 (m, 4H), 1.56 - 1.46 (m, 1H), 1.04 (t, J = 8.0 Hz, 3H).

Example S89A and S89B

(3S,8S)-8-[[(7S)-7-[3-amino-2-fluoro-5-prop-1-ynyl-6-(trifluoromethyl)phenyl]-4-[(1R,5S)-1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl]-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl]oxymethyl]-N-(4,6-dimethoxy-2-methyl-pyrimidin-5-yl)-1,2,3,5,6,7-hexahydropyrrolizine-3-carboxamide or

(3S,8S)-8-[[(7S)-7-[3-amino-2-fluoro-5-prop-1-ynyl-6-(trifluoromethyl)phenyl]-4-[(1S,5R)-1-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl]-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl]oxymethyl]-N-(4,6-dimethoxy-2-methyl-pyrimidin-5-yl)-1,2,3,5,6,7-hexahydropyrrolizine-3-carboxamide



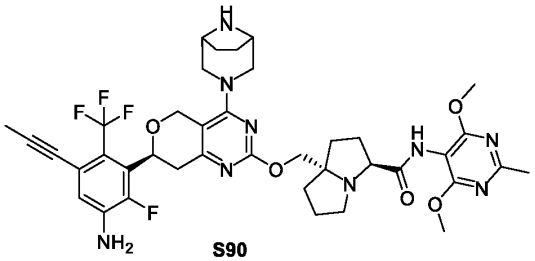
S89A or S89B

Compound **S89A** was prepared analogous to compound **S86A**, replacing (3S,7aS)-N-(1,3-dimethoxypropan-2-yl)-7a-(hydroxymethyl)hexahydro-1H-pyrrolizine-3-carboxamide with (3S,7aS)-N-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-7a-(hydroxymethyl)hexahydro-1H-pyrrolizine-3-carboxamide. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5mm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-80%) to afford compound **S89A**. LCMS: $[M+H]^+$ = 810.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 4.08 (d, *J* = 12.0 Hz, 1H), 4.00 - 3.96 (m, 1H), 3.94 (s, 6H), 3.56 - 3.51 (m, 2H) , 3.38 (d, *J* = 12.0 Hz, 1H), 3.23 - 3.18 (m, 1H), 3.12 - 3.08 (m, 1H), 2.93 - 2.80 (m, 3H), 2.50 (s, 3H), 2.23 - 2.16 (m, 1H) , 2.14 - 2.05 (m, 3H), 2.02 (s, 3H), 2.00 - 1.85 (m, 5H) , 1.80 - 1.74 (m, 1H), 1.72 - 1.64 (m, 1H) , 1.55 - 1.47 (m, 1H) , 1.31 (s, 3H).

Compound **S89B** was prepared analogous to compound **S86B**, replacing (3S,7aS)-N-(1,3-dimethoxypropan-2-yl)-7a-(hydroxymethyl)hexahydro-1H-pyrrolizine-3-carboxamide with (3S,7aS)-N-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-7a-(hydroxymethyl)hexahydro-1H-pyrrolizine-3-carboxamide. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 50%-60%) to afford compound **S89B**. LCMS: $[M+H]^+$ = 810.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.08 (d, *J* =12.0 Hz, 1H), 4.00 - 3.96 (m, 1H), 3.94 (s, 6H), 3.56 (d, *J* = 4.0 Hz, 1H), 3.46 (d, *J* =12.0 Hz, 1H), 3.26 - 3.16 (m, 2H), 3.12 - 3.08 (m, 1H), 2.99 (d, *J* =12.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.49 (s, 3H), 2.18 - 2.15 (m, 1H), 2.13 - 2.08 (m, 2H), 2.04 - 1.84 (m, 9H), 1.79 - 1.72 (m, 2H), 1.54 - 1.44 (m, 1H), 1.29 (s, 3H).

Example S90

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(4,6-dimethoxy-2-methylpyrimidin-5-yl)hexahydro-1H-pyrrolizine-3-carboxamide

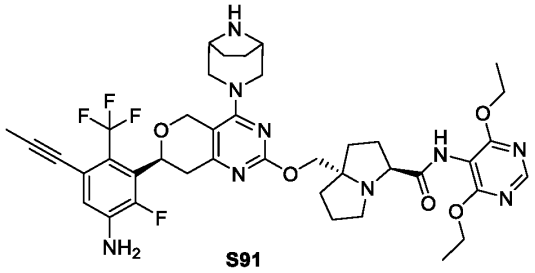


S90

Compound **S90** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 4,6-dimethoxy-2-methylpyrimidin-5-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-80%) to afford compound **S90**. LCMS: $[M+H]^+$ = 796.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.19 (d, J = 12.0 Hz, 1H), 4.15 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 8.0 Hz, 1H), 4.00 - 3.95 (m, 1H), 3.94 (s, 6H), 3.57 - 3.50 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.22 (dd, J = 20.0, 12.0 Hz, 1H), 3.12 - 3.08 (m, 1H), 3.05 (d, J = 12.0 Hz, 1H), 2.93 - 2.81 (m, 2H), 2.50 (s, 3H), 2.20 - 2.06 (m, 3H), 2.03 - 1.87 (m, 8H), 1.86 - 1.74 (m, 3H), 1.72 - 1.65 (m, 1H).

Example S91

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(4,6-diethoxypyrimidin-5-yl)hexahydro-1H-pyrrolizine-3-carboxamide

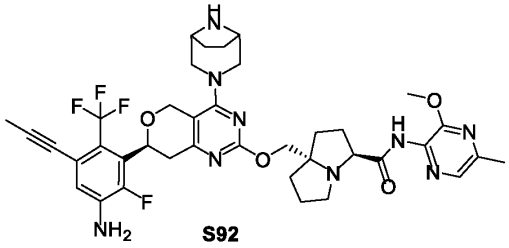


S91

Compound **S91** was prepared analogous to compound **16D** (CN 2024/083328), replacing N-ethyl-4-methoxybenzylamine with 4,6-diethoxypyrimidin-5-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 60%-80%) to afford Compound **S91**. LCMS: $[M+H]^+$ = 810.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.28 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.19 - 5.11 (m, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.47 - 4.38 (m, 4H), 4.21 - 4.07 (m, 3H), 4.02 - 3.97 (m, 1H), 3.56 - 3.50 (m, 3H), 3.45 - 3.39 (m, 1H), 3.26 - 3.13 (m, 2H), 3.07 - 3.02 (m, 1H), 2.95 - 2.82 (m, 2H), 2.22 - 2.08 (m, 3H), 2.04 - 1.90 (m, 8H), 1.85 - 1.66 (m, 4H), 1.35 (t, J = 8.0 Hz, 6H).

Example S92

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(3-methoxy-5-methylpyrazin-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide

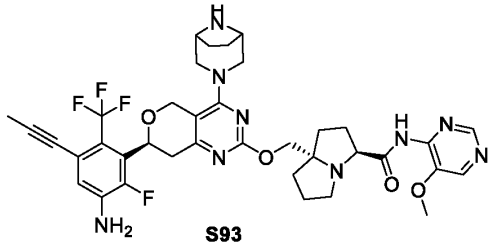


S92

Compound **S92** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 3-methoxy-5-methylpyrazin-2-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*30mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 45%-65%) to afford compound **S92**. LCMS: $[M+H]^+$ = 766.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.79 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 12.0, 4.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.21 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 8.0 Hz, 1H), 4.06 - 4.02 (m, 1H), 4.01 (s, 3H), 3.57 - 3.53 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.08 - 3.02 (m, 2H), 2.90 - 2.81 (m, 2H), 2.43 (s, 3H), 2.26 - 2.19 (m, 1H), 2.16 - 2.08 (m, 2H), 2.05 - 1.90 (m, 8H), 1.87 - 1.75 (m, 3H), 1.74 - 1.68 (m, 1H).

Example S93

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(5-methoxypyrimidin-4-yl)hexahydro-1H-pyrrolizine-3-carboxamide



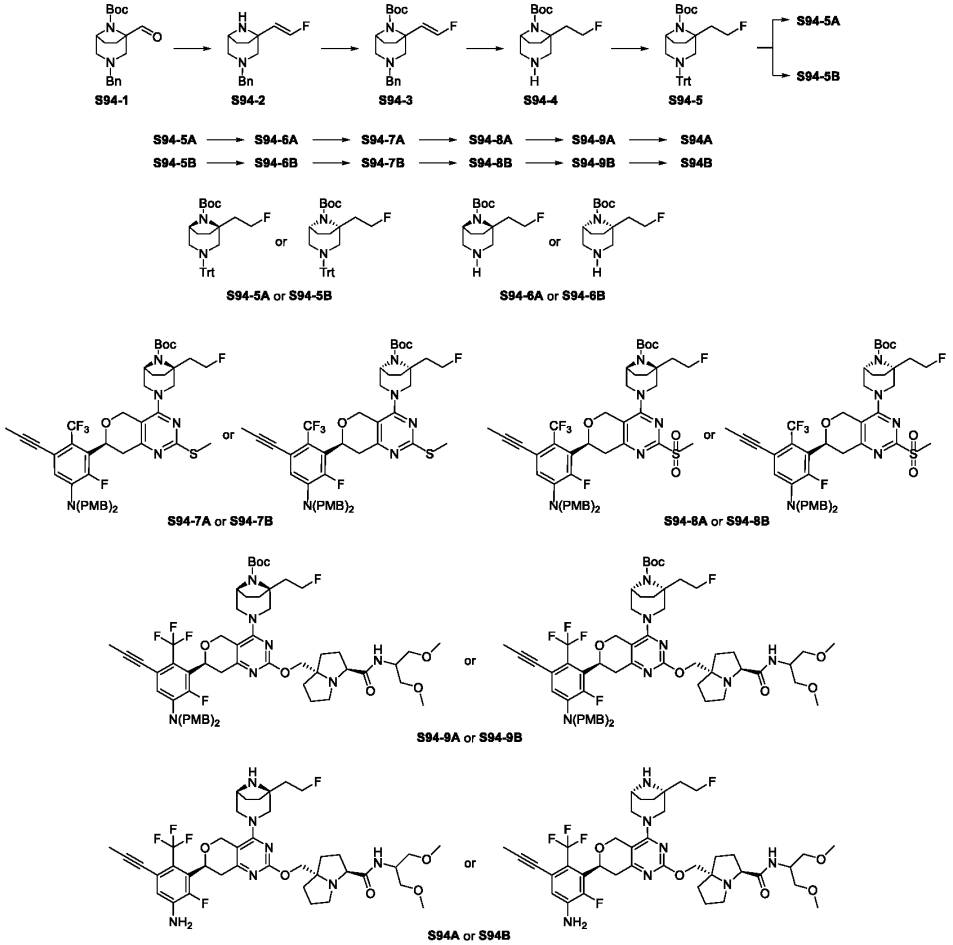
S93

Compound **S93** was prepared analogous to compound **56** (CN 2024/083328), replacing (*S*)-3,3-difluorocyclopentanamine hydrochloride with 5-methoxypyrimidin-4-amine. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **S93**. LCMS: $[M+H]^+$ = 752.5. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.50 (s, 1H), 8.38 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.15 (dd, J =

12.0, 4.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 4.16 - 4.09 (m, 3H), 4.01 (s, 3H), 3.57 - 3.50 (m, 3H), 3.43 (d, J = 12.0 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.07 - 2.98 (m, 2H), 2.90 - 2.76 (m, 2H), 2.29 - 2.21 (m, 1H), 2.17 - 2.07 (m, 2H), 2.04 - 1.90 (m, 8H), 1.85 - 1.66 (m, 4H).

Example S94A and **S94B**

(3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1S,5S)-1-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide or (3S,7aS)-7a-((((S)-7-(3-amino-2-fluoro-5-(prop-1-yn-1-yl)-6-(trifluoromethyl)phenyl)-4-((1R,5R)-1-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)oxy)methyl)-N-(1,3-dimethoxypropan-2-yl)hexahydro-1H-pyrrolizine-3-carboxamide



Step 1：S94-2

To a solution of compound **S94-1** (1.6 g, 4.84 mmol) in dry THF (20 mL) was added KHMDS (7.26 mL, 1 M in THF) dropwise at -78 °C. The mixture was stirred at -78 °C for 0.5 hours. Then 2-(fluoromethylsulfonyl)pyridine (890.7 mg, 5.08 mmol) was added and the reaction was stirred at -78 °C for an additional 3 hours. The reaction was quenched with saturated solution of NH_4Cl (5 mL), then HCl (5 mL, 3 M in water) was added. The resulting mixture was stirred at 50 °C for 2 hours. The reaction was quenched with saturated $NaHCO_3$ (30 mL) at 0 °C, extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S94-2**. LCMS: $[M+H]^+$ = 247.2.

Step 2: S94-3

To a solution of compound **S94-2** (1.1 g, 4.47 mmol) in DCM (15 mL) was added TEA (1.24 mL, 8.93 mmol) and Boc_2O (1.23 mL, 5.36 mmol). The reaction was stirred at 25 °C for 2 hours. The reaction was diluted with water (15 mL), extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EtOAc = 10:1) to afford compound **S94-3**. LCMS: $[M+H]^+$ = 347.2.

Step 3: S94-4

To a solution of compound **S94-3** (1 g, 2.89 mmol) in MeOH (20 mL) was added Pd/C (307.2 mg, 10% purity). The reaction was stirred at 25 °C for 2 hours under H_2 (1 atm) atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (5 mL × 3). The filtrate was concentrated under reduced pressure to afford crude compound **S94-4**. LCMS: $[M+H]^+$ = 259.2.

Step 4: S94-5 and **S94-5A & S94-5B**

To a solution of compound **S94-4** (740 mg, 2.86 mmol) in MeCN (4 mL) and DCM (4 mL) were added TEA (1.20 mL, 8.59 mmol) and triphenylmethyl chloride (878.42 mg, 3.15 mmol). The reaction was stirred at 25 °C for 16 hours. The reaction was diluted with water (10 mL), extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc = 10:1) to afford compound **S94-5**.

The compound **S94-5** was separated by preparative SFC (System: Waters SFC 150, Column name: Regis WHELK-O1(S,S)WHELK, Column size: 40*250mm, 10μm, Mobile Phase A: Supercritical CO_2, Mobile Phase B: MeOH + (0.05%) NH_3·MeOH; A/B = 70/30; Wavelength: 214 nm/254nm, Flow Rate: 100 mL/ minute, Column temp: rt; Cycle time: 6.94 min) to afford compound **S94-5A** and **S94-5B**. Analytical SFC method (column: DAICEL CHIRALPAK®WHELK-

3, 3.0*100 mm 3 μm, mobile phase A: Supercritical CO_2, mobile phase B: MeOH + (0.05%) DEA; A/B = 95/5). Compound **S94-5A**, Rt = 1.994 min, 99.48% ee; compound **S94-5B**, Rt = 2.361 min, 99.38% ee.

Step 5：S94-6A

To a solution of compound **S94-5A** (140 mg, 279.64 μmol) in THF (4 mL) was added HCl (838.92 μL, 1 M in water). The reaction was stirred at 25 °C for 5 hours. The reaction was adjusted with saturated solution of $NaHCO_3$ to pH = 7, extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude compound **S94-6A**. LCMS: $[M+H]^+$ = 259.2.

Steps 6~9：S94A

Compound **S94A** was prepared analogous to compound **S86A**, replacing intermediate **S86-2A** with intermediate **S94-6A**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **S94A**. LCMS: $[M+H]^+$ = 792.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.75 - 4.69 (m, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.63 - 4.54 (m, 1H), 4.23 - 4.12 (m, 3H), 4.07 (d, *J* = 8.0 Hz, 1H), 3.77 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.61 (d, *J* = 12.0 Hz, 1H), 3.55 (d, *J* = 8.0 Hz, 1H), 3.49 - 3.41 (m, 4H), 3.34 (s, 3H), 3.33 (s, 3H), 3.26 - 3.17 (m, 2H), 3.00 (d, *J* = 12.0 Hz, 1H), 2.97 - 2.93 (m, 1H), 2.85 (dd, *J* = 20.0, 4.0 Hz, 1H), 2.76 - 2.70 (m, 1H), 2.17 - 2.04 (m, 3H), 2.04 - 2.00 (m, 4H), 1.99 - 1.84 (m, 7H), 1.81 - 1.67 (m, 2H), 1.61 - 1.54 (m, 1H).

Compound **S94B** was prepared analogous to compound **S94A**, replacing intermediate **S94-5A** with intermediate **S94-5B**. The crude product was purified by Prep-HPLC (Chromatographic columns: Waters Xbridge 250*19mm, 5μm, ACN-H_2O (0.1% NH_3); Gradient: (ACN): 40%-70%) to afford compound **S94B**. LCMS: $[M+H]^+$ = 792.6. ^1H NMR (400 MHz, CD_3OD) δ ppm 6.90 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.77 - 4.72 (m, 1H), 4.68 - 4.60 (m, 2H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.22 - 4.17 (m, 2H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.83 - 3.75 (m, 1H), 3.56 - 3.43 (m, 6H), 3.40 (d, *J* = 12.0 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.21 (dd, *J* = 20.0, 12.0 Hz, 1H), 3.01 - 2.92 (m, 1H), 2.89 - 2.82 (m, 2H), 2.77 - 2.71 (m, 1H), 2.18 - 2.05 (m, 4H), 2.02 (s, 3H), 1.99 - 1.82 (m, 7H), 1.78 - 1.70 (m, 1H), 1.68 - 1.54 (m, 2H).

Biological Test Data

Experimental Example 1. AsPC-1 cell p-ERK inhibition test

1. Purpose:

The inhibitory activity of the compound on p-ERK levels of $KRAS^{G12D}$-mutant pancreatic cancer AsPC-1 cells was assessed by HTRF.

2. Experimental materials:

ASPC-1 cells were purchased from ATCC; RPMI-1640 medium was purchased from Gibco; Fetal Bovine Serum was purchased from Hyclone; Advanced Phospho-ERK1/2(THR202/TYR204) KIT was purchased from Bioauxilium-

Table B-1. Advanced Phospho-ERK1/2(THR202/TYR204) KIT Component Table

Component Name	Storage Temperature
Advanced PhosphoERK1/2 Eu Cryptate antibody	≤ -16°C
Advanced PhosphoERK1/2 d2 antibody	≤ -16°C
Blocking reagent (stock solution 100X)	≤ -16°C
Lysis buffer # 1 (stock solution 4X)	≤ -16°C
Detection buffer (ready-to-use)	≤ -16°C

3. Experimental method:

ASPC-1 cells were seeded in a 384-well cell culture plate with a white bottom, 8 μL of cell suspension per well, containing 7,500 cells per well, and the cell plates were placed in a carbon dioxide incubator and incubated at 37°C overnight;

The test compound was diluted to 3 mM with 100% DMSO as the first concentration, and then diluted to ten concentrations of 3000, 1000, 300, 100, 30, 10, 3, 1, 0.3, 0.1 μM with a pipette. Take 2 μL of compound and add 198 μL of cell starvation medium. After mixing well, take 15 μL of compound solution and add 35 μL of cell starvation medium and mix well. Then add 4 μL of compound solution in each well to the corresponding cell plate well. Place the cell plate back in the carbon dioxide incubator for continued incubation for 3 hours. At this time, the compound concentration is 3,000, 1,000, 300, 100, 30, 10, 3, 1, 0.3, 0.1 nM.

After the end of incubation, add 3 μL of 5X cell lysate to each well, and incubate at room temperature for 30 minutes;

Dilute Phospho-ERK1/2 Eu Cryptate antibody and Phospho-ERK1/2 d2 antibody 20-fold by using Detection buffer, mix well in a 1:1 ratio, add 5 μL to the cell culture plate per well, and incubate at room temperature for 2 h.

After the end of incubation, use a multi-label analyzer to read HTRF excitation: 320 nm, emission: 615 nm, 665 nm;

4. Data analysis:

The raw data was converted to inhibition rate by applying the equation (Sample-Min)/(Max-Min)*100%, and the value of IC50 can be obtained by curve fitting with four parameters log(inhibitor) vs. response -- Variable slope Surf mode in GraphPad Prism. Table B-2 provides the inhibition of p-ERK by the compounds of the present invention.

Max well: Positive control well read value is 1X lysate

Min well: Negative control well reads 0.5% DMSO well cell lysate

5. Experimental results:

See Table B-2 for the results.

Table B-2 IC_{50} values of compound inhibition on p-ERK of AsPC-1 cells

Compound Number	AsPC-1 p-ERK IC_{50} (nM)
Hydrochloride of Compound **1**	164
Trifluoroacetate of Compound **3A**	28.9

Experimental conclusion: The compounds of the present invention have a significant inhibitory effect on the p-ERK of $KRAS^{G12D}$ mutant AsPC-1 cells.

Experimental Example 2. AsPC-1 cell p-ERK inhibition test

Experimental materials:

1640 medium, penicillin/streptomycin antibiotics were purchased from Gibco, and fetal bovine serum was purchased from Biosera. CellTiter-Glo (Cell Viability Chemiluminescence Detection Reagent) reagent was purchased from Promega. AsPC-1 cell line was purchased from ATCC, Envision Multi-Tag Analyzer (PerkinElmer).

Experimental method:

AsPC-1 ($KRAS^{G12D}$ mutation, pancreatic cancer) cells were seeded in ultra-low adsorption 96-well blackwall plate, 80 μL cell suspension per well, containing 10,000 AsPC-1 cell lines from ATCC cells. Plates were incubated overnight in a carbon dioxide incubator.

The test compound was diluted 8 concentrations with a 5-fold drain, i.e., from 2 mM to 25.6 nM, and a double replicate well experiment was set up. Add 78 μL of culture medium to the intermediate plate, and transfer 2 μL of gradient diluted compound per well to the intermediate plate according to the corresponding positions. Mix well and transfer 20 μL of each well to the cell plate. Compound concentrations transferred to the cell plate ranged from 10 μM to 0.128 nM. The cell plates were incubated in a carbon dioxide incubator for 10 days. Another cell plate was prepared, and the signal value was read as the maximum value (Max value in the equation below) on the day of dosing to participate in the data analysis.

Each 100 μL of cell viability chemiluminescence detection reagent was added to the cell plate and

incubated at room temperature for 30 minutes to stabilize the luminescence signal. Use multi-label analyzer for reading.

Data analysis:

The raw data was converted to inhibition rate by applying the equation (Sample-Min)/(Max-Min)*100%, and the value of IC50 can be obtained by curve fitting with four parameters "log(inhibitor) vs. response -- Variable slope" Surf mode in GraphPad Prism. Table B-3 provides the inhibitory activity of the compound of the present invention on pERK levels in AsPC-1 cells.

Table B-3 IC_{50} values of compound inhibition on p-ERK in AsPC-1 cells

Compound Number	AsPC-1 p-ERK IC_{50} (nM)
Trifluoroacetate of Compound **5A**	7.4
Trifluoroacetate of Compound **7**	24.9
Trifluoroacetate of Compound **12**	35.0

Experimental conclusion: The compounds of the present invention have a significant inhibitory effect on the p-ERK of $KRAS^{G12D}$ mutant AsPC-1 cells.

Experimental Example 3. AsPC-1, Panc0403 cell p-ERK inhibition test

Experimental method:

On the first day, 6000/well APC-1 (ATCC, CRL-1682, $KRAS^{G12D}$ mutation, pancreatic cancer) or PANC04.03 (ATCC, CRL-2555, $KRAS^{G12D}$ mutation, pancreatic cancer) were incubated in 384-well plates (Corning, 354663) overnight at 37°C in an incubator with 5% CO_2. The next day, serially diluted compounds were added to cell plates (DMSO content of 0.1%) with echo 655, incubated at 37°C with 5% CO_2 for 1.5 hours. Add 40 μL of 8% cell tissue fixative and fix at room temperature for 20 minutes. Discard the supernatant and wash twice with PBS for two minutes each. Add 40 μL of methanol and permeabilize at room temperature for 10 minutes. Discard the supernatant and wash twice with PBS for two minutes each. Add 20 μL of fixative and block at room temperature for 1 hour. Discard the supernatant and add 20 μL of prepared primary antibody diluent (1: 1000-diluted Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) XP® Rabbit mAb and 1: 2000 diluted GAPDH(D4C6R) Mouse mAb), incubated overnight in a 4°C refrigerator. On the third day, the primary antibody was discarded and washed 3 times with 1xPBST for 3 minutes each. Add the prepared secondary antibody diluent (1: 2000 diluted IRDye 800CW Goat anti-Rabbit IgG (H+L) (0.5 mg) and 1: 2000 diluted IRDye 680RD Goat anti Mouse IgG (H+L) (0.5 mg)) and incubated at room temperature for 1 hour away from light. The secondary antibody was discarded and washed 3 times with 1xPBST for 3 minutes each. The pERK and GAPDH signals were quantified at 800 nM and 700 nM, respectively, by using a Li-Cor Odyssey machine after 1 minute of inversion 10000 centrifugation.

Experimental results

See Table B-4 for the results.

Table B-4 IC_{50} values of compound inhibition on p-ERK of AsPC-1 and Panc0403 cells

Compound Number	**AsPC-1 p-ERK IC_{50} (nM)**	**Panc0403 p-ERK IC_{50} (nM)**
Trifluoroacetate of Compound **4B**	5.6	9.0
Trifluoroacetate of Compound **9B**	12	21.1
Trifluoroacetate of Compound **10**	9.3	19.7
Trifluoroacetate of Compound **13A**	6.1	7.8
Trifluoroacetate of Compound **14B**	19.4	23.9
Trifluoroacetate of Compound **15B**	5.3	5.0
Compound **16D**	1.9	4.5
Compound **17D**	22.4	23.8
Compound **18D**	3.2	6.9
Formate of Compound **19D**	1.1	3.6
Compound **20D**	0.4	1
Formate of Compound **21D**	10.9	13.7
Compound **22D**	1.3	4.2
Compound **23D**	0.6	2.1
Formate of Compound **24D**	4.7	8.2
Compound **25B**	110	121
Compound **27D**	6.2	12.6
Hydrochloride of Compound **28B**	35.1	33.3
Formate of Compound **29**	43.8	27.0
Compound **30**	>1000	592.0
Compound **31**	190.0	335.0
Hydrochloride of Compound 32	628.0	371.2
Compound 33A	305.0	157.7
Compound 33B	273.0	84.2
Compound 34	560.0	257.3

Hydrochloride of Compound 35A	113.0	50.9
Hydrochloride of Compound 35B	42.0	11.9
Formate of Compound 36B	44.7	98.7
Formate of Compound 36C	30.3	72.2
Formate of Compound 36D	6.2	12.4
Hydrochloride of Compound 37A	251.4	576.6
Hydrochloride of Compound 37B	31.0	61.4
Hydrochloride of Compound 38	3.7	4.1
Formate of Compound 39A	77.7	162.0
Formate of Compound 39B	1066.9	1932.8
Compound 39C	12.0	22.7
Compound 40A	2166.1	3898.3
Formate of Compound 40B	564.3	1007.1
Compound 41C	1356.6	1847.7
Formate of Compound 41D	274.0	392.9
Formate of Compound 42D	25.9	44.7
Compound 43	5741.0	8645.0
Compound 44A	137.5	114.6
Formate of Compound 44B	2802.0	523.9
Compound 45	>1000	>10000
Hydrochloride of Compound 46	1162.0	331.8
Compound 47	142.0	57.4
Formate of Compound 48	600.6	2179.4
Compound 49	100.3	135.8
Formate of Compound 50	52.0	132.6
Compound 51	2959.7	>10000
Hydrochloride of Compound 52	179.6	437.3
Formate of Compound 53A	33.9	34.6
Formate of Compound 53B	1143.2	1396.3

Compound 54A	557.7	457.7
Formate of Compound 54B	9284.9	>10000
Formate of Compound 55	5449.9	9852.7
Compound 58	1.2	2.6
Compound 59	1.4	2.9
Compound 60	2789.2	4865.6
Compound 61	1115.5	1732.5
Compound 42C	249.6	399.7
Compound 62	0.9	1.3
Hydrochloride of Compound 63	19.6	33.1
Compound 64	95.2	285.1
Compound 65	8.5	19.0
Formate of Compound 66	3140.8	6966.0
Compound 67	5767.6	>10000
Compound 68	0.7	1.8
Compound 69	16.5	21.4
Formate of Compound 70A1	5600.4	>10000
Formate of Compound 70A2	>10000	>10000
Formate of Compound 70B1	559.4	1220.6
Formate of Compound 70B2	866.5	1977.1
Compound 70C	10.1	15.8
Compound 71	3179.4	>10000
Compound 72	54.5	124.6
Compound 73	2.4	4.0
Compound 74	2.1	3.5
Compound 75	33.8	63.5
Compound 76	0.9	1.8
Compound 77	0.7	1.4
Compound 78	0.9	1.8
Compound 79	6.9	16.1
Compound 80	1.6	3.6

Compound 81	3.8	5.3
Compound 82B	1.0	1.8
Compound 82A	37.8	94.6
Compound 83	0.7	1.4
Compound 84	6.3	13.6
Formate of Compound 85	1855.5	3770.3
Compound 86	12.1	17.5
Compound 87	212.4	338.9
Compound 88	1.7	2.9
Compound 89	0.9	1.4
Compound 90	1.6	2.3
Compound 91	5366.1	5439.3
Compound 92	933.3	1489.4
Compound 93	51.0	60.9
Compound 94	294.4	448.6
Compound 95	2.6	4.8
Compound 96A	1.5	2.8
Compound 96B	3.0	3.3
Compound 97	3.3	4.5
Compound 98	>10000	>10000
Compound 99	>10000	>10000
Compound 100A	1078.2	1642.3
Compound 100B	7.6	6.3
Compound 101	2563.1	3108.3
Compound 102	2.4	2.7
Compound 57	1.2	1.6
Compound 103	28.5	28.3
Compound 104	3.4	3.3
Compound 105	4.2	4.1
Compound 106	3.1	3.7
Formate of Compound 107	3.4	7.1

Compound 108	5.0	7.5
Compound 109B	1.9	2.8
Compound 109A	235.3	658.2
Compound 110	695.9	1405.3
Compound 111	2.5	4.3
Compound 112	74.6	131.7
Compound 113	1.2	2.2
Compound 56	0.5	1.2
Compound 114	0.6	1.1
Compound 115	564.7	1091.8
Compound 116	5.2	14.2
Compound 117	3.1	4.6
Compound 118	114.5	169.5
Compound 119A	2236.8	9032.0
Compound 119B	2996.5	>10000
Compound 120A	12.0	37.7
Compound 120B	2.0	5.0
Compound 121	55.2	75.4
Formate of Compound 122A	73.9	94.9
Formate of Compound 122B	59.7	54.4
Formate of Compound 122C	90.4	123.5
Formate of Compound 122D	9.0	11.1
Compound 123	934.3	1703.1
Compound 124A	172.5	344.7
Compound 124B	42.8	39.5
Formate of Compound 125	7.6	7.3
Compound 126	2.0	2.9
Compound 127	1.3	1.4
Compound 128	2.2	2.4
Compound 129	77.4	124.7
Compound 130	4.3	5.0

Compound 131	14.8	28.6
Compound 132	2.0	5.1
Compound 133	9.9	21.0
Compound 134	15.6	41.6
Compound 135	24.8	45.6
Compound 136	2.7	5.1
Compound 137	649.2	1300.6
Compound 138	4.5	12.5
Compound 139	4.3	11.4
Formate of Compound 140A	30.3	57.7
Formate of Compound 140B	60.2	113.7
Compound 141	0.6	1.2
Compound 142	0.4	0.9
Compound 143	2.1	4.2
Compound 144	2.0	5.3
Compound 145	0.3	0.7
Compound 146	0.3	0.7
Compound 147	3.4	10.0
Compound 148	162.2	266.1
Compound 149	>10000	>10000
Compound 150	1.2	2.8
Compound 151	0.5	1.3
Compound 152	39.8	61.6
Compound 153	0.6	1.4
Compound 154	0.7	1.5
Compound 155	4.8	11.0
Compound 156A	0.4	0.8
Compound 157	1.9	3.6
Compound 158A	0.5	1.1
Compound 159	2.2	3.6
Compound 160	0.7	1.5

Compound 161	0.8	2.4
Compound 162A	2.1	4.5
Compound 162D	2.1	4.7
Compound 163	0.3	0.7
Compound 164	12.2	30.9
Compound 165	6.4	15.4
Formate of Compound 166	1.4	2.9
Compound 167	62.8	122.6
Compound 168A	4.4	8.2
Compound 168B	4.0	8.5
Compound 156B	0.4	0.7
Compound 158B	0.7	1.1
Compound 162B	1.8	2.0
Compound 162C	3.1	4.1
Compound S1	0.69	0.96
Compound S2	0.88	1.52
Compound S3	1.61	2.02
Compound S4	3.89	6.91
Compound S5	78.43	150.65
Compound S6	1.12	1.64
Compound S7	3.83	4.98
Compound S8	2.64	3.86
Compound S9	0.97	1.43
Compound S10	0.43	0.64
Compound S11	0.64	0.99
Compound S12	0.53	0.75
Compound S13	1.14	1.78
Compound S14	1.26	1.53
Compound S15	3.1	3.93
Compound S16	2.1	3.33
Compound S17	2.62	4.1

Compound S18A	0.81	1.26
Compound S18B	0.76	1.07
Compound S19A	3.58	9.46
Compound S19B	6.42	10.98
Compound S20	1.9	4.07
Compound S21	4.09	12.41
Compound S22	13.61	28.43
Compound S23	4.05	11.68
Compound S24	1.33	2.62
Compound S25	31.96	58.94
Compound S26	45.88	61.84
Compound S27	0.47	1.47
Compound S28	0.36	0.98
Compound S29	0.39	1.05
Compound S30	47.11	96.7
Compound S31	14.11	32.12
Compound S32	0.63	1.79
Compound S33	0.47	1.44
Compound S34	0.45	1.37
Compound S35	11.58	25.61
Compound S36	0.95	2.48
Compound S37	0.61	1.79
Compound S38	3	6.05
Compound S39	0.49	0.98
Compound S40	0.65	1.28
Compound S41	0.42	0.87
Compound S42	0.71	1.32
Compound S43	6	7.35
Compound S44	0.68	0.84
Compound S45	0.68	1.03
Compound S46	0.71	1.75

Compound S47	1.45	2.5
Compound S48	0.53	1.33
Compound S49	0.78	1.42
Compound S50A	0.69	1.5
Compound S50B	0.51	1.36
Compound S51	1.09	1.67
Compound S52	0.96	1.61
Compound S53	1.53	2.45
Compound S54	1.51	2.49
Compound S55	0.65	1.04
Compound S56	202.81	491.03
Compound S57	1.31	1.75
Compound S58	1.86	3.01
Compound S59	2.13	3.75
Compound S60	3.6	4.7
Compound S61	3.03	4.14
Compound S62	4.54	7.24
Compound S63A	1.06	1.68
Compound S63B	1.6	5.03
Compound S64	316.12	370.59
Compound S65	28.96	36.93
Compound S66	8.87	9.65
Compound S67A	3.33	4.27
Compound S67B	2.09	3.86
Compound S68A	2.14	3.54
Compound S68B	1.85	3.65
Compound S69	0.74	1.4
Compound S70	1.39	2.46
Compound S71	0.95	1.29
Compound S72	125.85	221.42
Compound S73A	0.29	0.77

Compound S73B	0.58	1.54
Compound S74	1.17	2.78
Compound S75	0.92	2.01
Compound S76	1063.9	2058.03
Compound S77	1.26	3.61
Compound S78	0.41	0.98
Compound S79	0.64	2.04
Compound S80	38.59	55.72
Compound S81	0.66	1.3
Compound S82	0.87	1.93
Compound S83	1.59	3.55
Compound S84	0.97	1.47
Compound S85	0.51	2.2
Compound S86A	0.62	1.39
Compound S86B	0.62	1.47
Compound S87	1.01	2.4
Compound S88A	1.73	8.96
Compound S88B	0.51	1.64
Compound S89A	1.49	4.18
Compound S89B	2.95	9.29
Compound S90	1.63	4.23
Compound S91	1.6	3.61
Compound S92	0.89	2.84
Compound S93	1.88	4.39
Compound S94A	1.87	4.32
Compound S94B	0.72	1.26

Experimental conclusion: The compounds of the present invention have a significant inhibitory effect on the p-ERK of $KRAS^{G12D}$ mutant AsPC-1 and Panc0403 cells.

Experimental Example 4. AsPC-1, Panc0403 cell proliferation inhibition test

Experimental method:

ASPC-1 (ATCC, CRL-1682, $KRAS^{G12D}$ mutation, pancreatic cancer) and PANC04.03 (ATCC,

CRL-2555, $KRAS^{G12D}$ mutation, pancreatic cancer) cells were inoculated into CellCarrier-96 ULA/CS plate (PE, 6055330) at a density of 2,000 cells/well/195 μL, and the diluted compound was added to the cell plate and cultured in a 37°C cell incubator for 7 days. CellTiter-Glo® 3D Detection Kit (3D-CTG, Promega, G9683) was left with cells at room temperature for 30 min, an equal volume of CTG was added to the assay plate and shaken for 20 min for cell lysis; cells were left at room temperature for 1 h and the luminescent signal was read using BMG (PHERAstar FSX). The percent compound viability of the treated wells was calculated between the control and blank groups. Wells containing cell culture medium were used as blank groups, and wells containing cells and the same percentage of DMSO were used as control groups.

Inhibition rate (%) = (control luminescent reading - compound treated well luminescent reading)/(control luminescent reading - blank luminescent reading) * 100%; then data were analyzed by fitting a 4-parameter logic model or Excel to calculate IC_{50} values, which were concentrations at 50% inhibition on the curve.

Experimental results

See Table B-5 for the results.

Table B-5 IC_{50} values of compound inhibition of AsPC-1 and Panc0403 cell proliferation

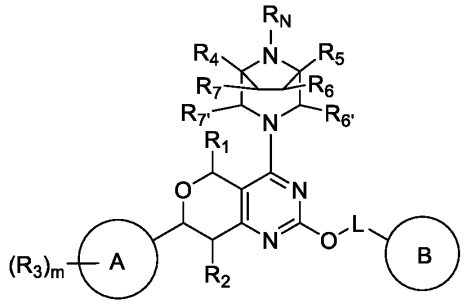
Compound Number	AsPC-1 IC_{50} (nM)	Panc0403 IC_{50} (nM)
Trifluoroacetate of Compound **4B**	34.3	295
Trifluoroacetate of Compound **9B**	48.5	409
Trifluoroacetate of Compound **10**	55.7	415
Trifluoroacetate of Compound **13A**	20.7	142
Trifluoroacetate of Compound **14B**	96.5	414
Trifluoroacetate of Compound **15B**	6.0	97
Compound **16D**	2.3	15.5
Compound **17D**	67.3	644
Compound **18D**	2.8	12.6
Formate of Compound **19D**	2.9	7.9
Compound **20D**	0.7	3.7
Formate of Compound **21D**	2.1	6.8
Compound **22D**	3.4	14.1
Compound **23D**	1.7	5.3
Formate of Compound **24D**	6.3	54
Compound **25B**	124	
Compound **27D**	8.7	71.4

Hydrochloride of Compound **28B**	69.8	124

Experimental conclusion: The compounds of the present invention have significant anti-proliferative inhibitory effects on $KRAS^{G12D}$ mutant AsPC-1 and Panc0403 cells.

CLAIMS

1. A compound of Formula (I') or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



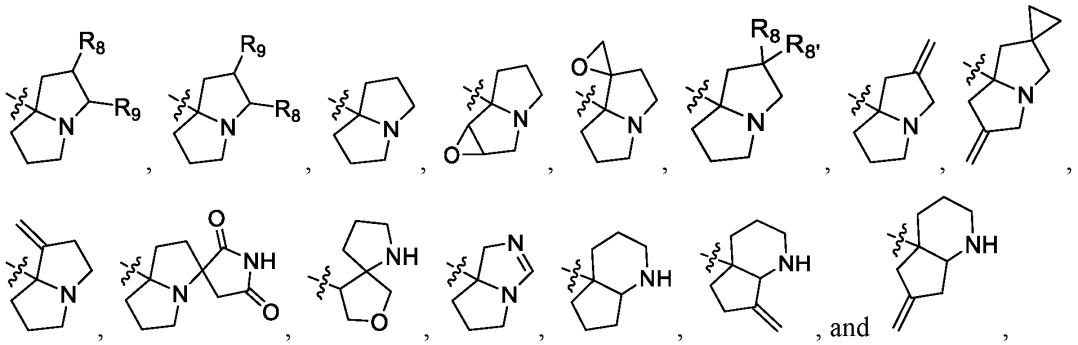
(I'),

wherein,

R_N is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 F or Cl;

Ring A is selected from C_6 aryl and 5-6 membered heteroaryl;

Ring B is selected from



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is selected from $-C(R_{L1}R_{L2})-$, wherein R_{L1} and R_{L2} are each independently selected from H, D, and C_{1-3} alkyl;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, -C(=O)-R_d, -C(=O)-$NR_{b1}R_{b2}$, and =NO(C_{1-3} alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and -C(=O)-$NR_{b1}R_{b2}$;

R_8 is selected from H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or, R_8 and $R_{8'}$ together with the carbon atom to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the C_{3-5} cycloalkyl and 3-5 membered heterocyclyl are each independently optionally substituted with 1, 2, or 3 R_{10};

R_9 is selected from -C(=O)-$NR_{b3}R_{b4}$ and -CH_2R_c;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, -C(=O)-R_d, -S-R_d, -S(=O)-R_d, -$S(=O)_2$-R_d, -NH-C(=O)-R_d, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH or F, and the C_{6-10} aryl and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1};

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, or 4 R_{e1};

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2, 3, or 4 R_{e1};

R_{b3} and R_{b4} are each independently selected from H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, or 4 R_{e2};

or, R_{b3} and R_{b4} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl is optionally substituted with 1, 2,

3, or 4 R_{e2};

R_c is selected from F, Cl, Br, I, OH, NH_2, -(C=O)$NR_{C1}R_{C2}$, -O(C=O)$NR_{C1}R_{C2}$, -NR_{C0}(C=O)R_{C1}, and -NR_{C0}(C=O)$NR_{C1}R_{C2}$;

R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

R_d is selected from C_{1-3} alkyl;

R_{e1} is selected from F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), -(C=O)N(C_{1-3} alkyl)$_2$, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl;

R_{e2} is selected from F, Cl, Br, I, OH, NH_2, NO_2, C_{1-3} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), -(C=O)N(C_{1-3} alkyl)$_2$, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s1}, and wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_{s2};

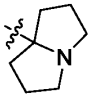
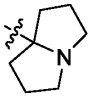
or, two R_{e2} together with the carbon atoms to which they are attached form a C_6 aryl or 5- or 6-membered heteroaryl;

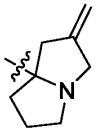
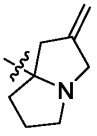
R_{s1} is selected from oxo, F, Cl, Br, I, OH, NH_2, NO_2, C_{1-6} alkyl, C_{1-6} alkylamino, di-C_{1-6} alkylamino, CN, C_{1-6} alkoxy, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), and -(C=O)N(C_{1-3} alkyl)$_2$;

R_{s2} is selected from F, Cl, Br, I, OH, NH_2, C_{1-6} alkylamino, di-C_{1-6} alkylamino, CN, C_{1-6} alkoxy, -S(=O)$_2$-(C_{1-3} alkyl), -(C=O)(C_{1-3} alkyl), -(C=O)O(C_{1-3} alkyl), -(C=O)NH(C_{1-3} alkyl), and -(C=O)N(C_{1-3} alkyl)$_2$; and

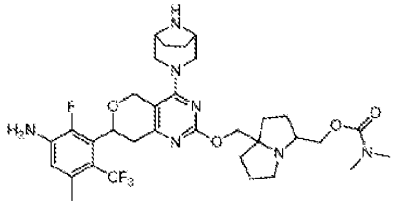
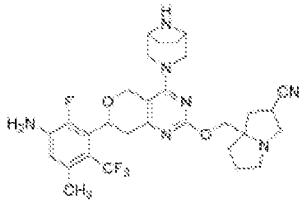
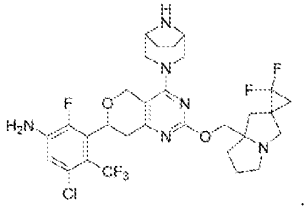
m is selected from 0, 1, 2, 3, 4, and 5;

provided that,

1) when Ring B is selected from , and the  is substituted with 1 R_{10}, and R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H;

2) when Ring B is selected from  , and the  is optionally substituted with 1, 2, 3, or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H; and

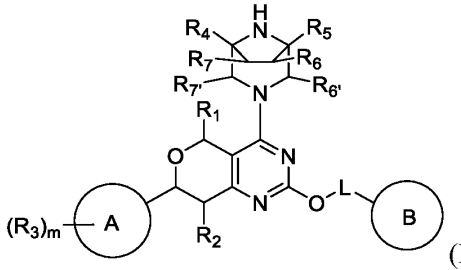
3) the compound is not

 ,  and  .

2. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according claim 1, wherein R_N is H.

3. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according claim 1, wherein R_N is C_{1-3} alkyl optionally substituted with 1, 2, or 3 F or Cl.

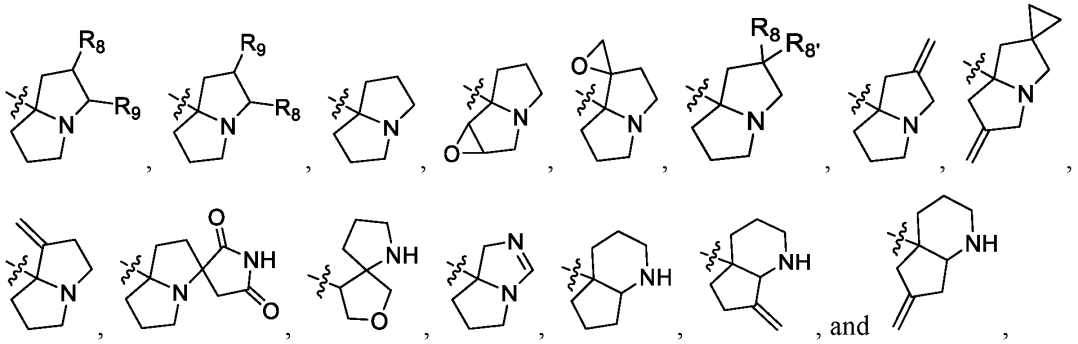
4. A compound of Formula (I') or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:


(I'),

wherein,

Ring A is selected from C_6 aryl and 5-6 membered heteroaryl;

Ring B is selected from



wherein Ring B is optionally substituted with 1, 2, 3, or 4 R_{10};

L is selected from -CH_2-, wherein the -CH_2- is optionally substituted with 1 or 2 D;

R_1 and R_2 are each independently selected from oxo, H, F, Cl, Br, I, and CN;

each R_3 is independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{3-5} cycloalkyl are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

each R_a is independently selected from D, F, Cl, Br, and I;

R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are each independently selected from oxo, H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, -C(=O)-R_d, -C(=O)-$NR_{b1}R_{b2}$, and =NO(C_{1-3} alkyl), wherein the C_{1-3} alkyl, C_{2-4} alkenyl, and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_b;

or, R_6 and R_7 together with the carbon atoms to which they are attached form a 3-5 membered heterocyclyl;

each R_b is independently selected from D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkoxy, and -C(=O)-$NR_{b1}R_{b2}$;

R_8 is selected from H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are each independently optionally substituted with 1, 2, 3, 4, or 5 R_a;

or, R_8 and $R_{8'}$ together with the carbon atom to which they are attached form a C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the C_{3-5} cycloalkyl and 3-5 membered heterocyclyl are each independently optionally substituted with 1, 2, or 3 R_{10};

R_9 is selected from -C(=O)-$NR_{b1}R_{b2}$ and -CH_2R_c;

each R_{10} is independently selected from oxo, D, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, di-C_{1-3} alkylamino, -S-R_d, -S(=O)-R_d, -$S(=O)_2$-R_d, and -NH-C(=O)-R_d,

wherein the C_{1-3} alkyl is optionally substituted with 1, 2, or 3 OH;

R_{b1} and R_{b2} are each independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each independently optionally substituted with 1, 2, or 3 R_{e1};

or, R_{b1} and R_{b2} together with the nitrogen atom to which they are attached form a 3-6 membered heterocyclyl;

R_c is selected from F, Cl, Br, I, OH, NH_2, $-O(C=O)NR_{C1}R_{C2}$, $-NR_{C0}(C=O)R_{C1}$, and $-NR_{C0}(C=O)NR_{C1}R_{C2}$;

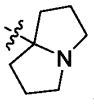
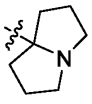
R_{C0}, R_{C1}, and R_{C2} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocyclyl;

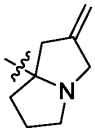
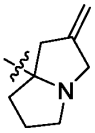
R_d is selected from C_{1-3} alkyl;

R_{e1} is selected from F, Cl, Br, I, OH, NH_2, C_{1-3} alkylamino, di-C_{1-3} alkylamino, CN, C_{1-3} alkoxy, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl; and

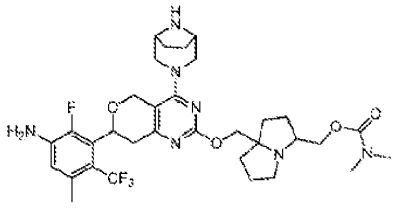
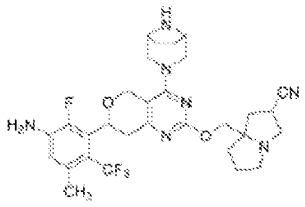
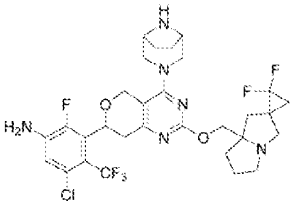
m is selected from 0, 1, 2, 3, 4, and 5;

provided that,

1) when Ring B is selected from , and the  is substituted with 1 R_{10}, and R_{10} is F, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H;

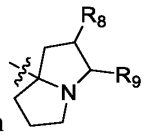
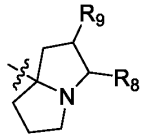
2) when Ring B is selected from , and the  is optionally substituted with 1, 2, 3, or 4 R_{10}, at least one of R_1, R_2, R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ is not H; and

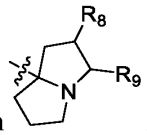
3) the compound is not

,  and .

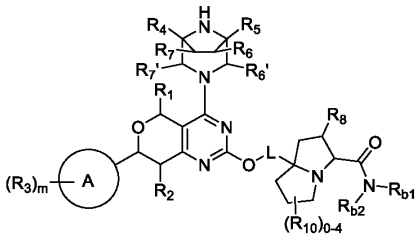
5. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein Ring A is selected from C_6 aryl.

6. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein Ring A is selected from 5-membered heteroaryl.

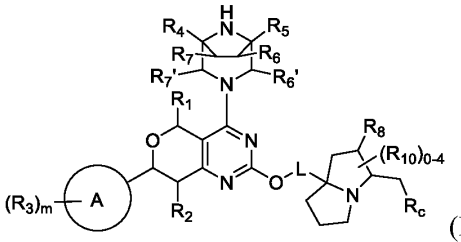
7. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-6, wherein Ring B is selected from  and , and is optionally substituted with 1, 2, 3, or 4 R_{10}.

8. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein Ring B is selected from , and is optionally substituted with 1, 2, 3, or 4 R_{10}.

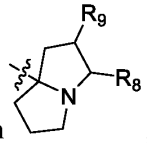
9. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 8, selected from a compound of Formula (I'-1-i) or a stereoisomers thereof, or a pharmaceutically acceptable salts thereof,


(I'-1-i).

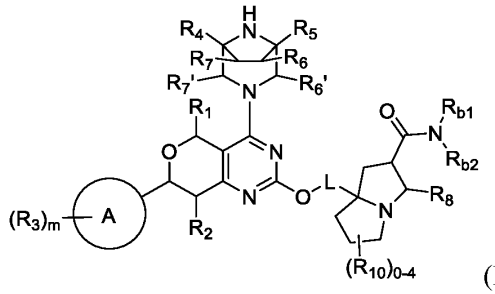
10. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 8, selected from a compound of Formula (I'-2-i) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



(I'-2-i).

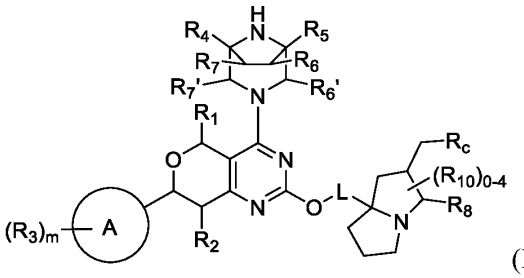
11. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein Ring B is selected from  , and is optionally substituted with 1, 2, 3, or 4 R_{10}.

12. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 11, selected from a compound of Formula (I'-1-ii) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

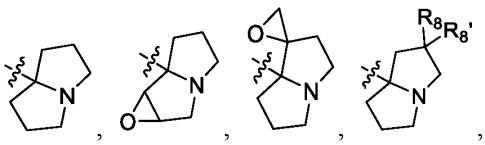
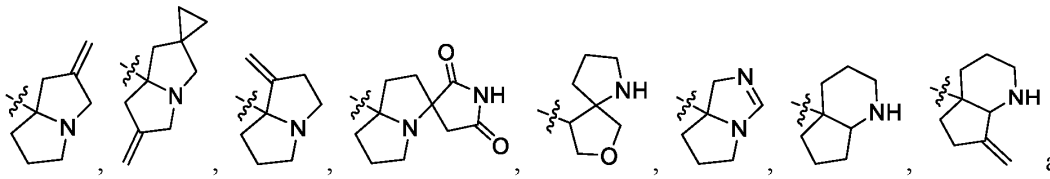
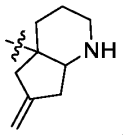


(I'-1-ii).

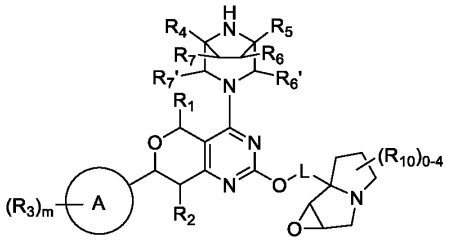
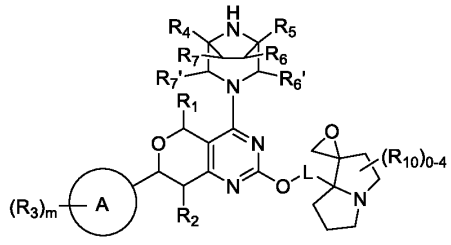
13. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 11, selected from a compound of Formula (I'-2-ii) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

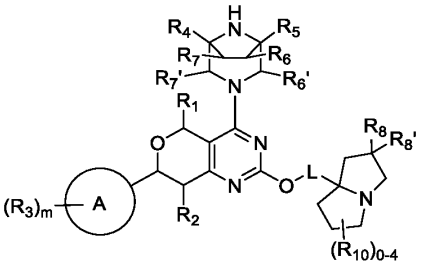
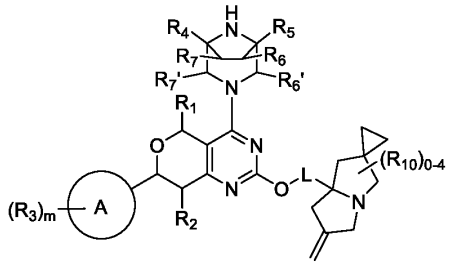


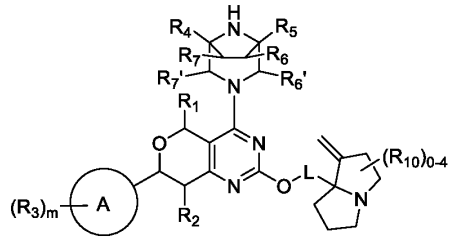
(I'-2-ii).

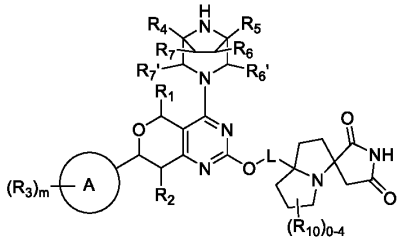
14. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-6, wherein Ring B is selected from , , and , and is optionally substituted with 1, 2, 3, or 4 R_{10}.

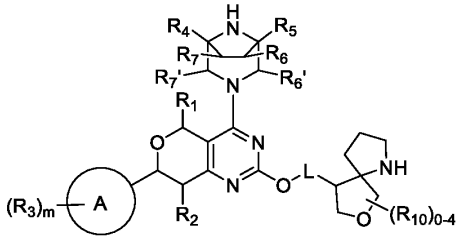
15. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 14, selected from a compound of Formula (I'-3), (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9), (I'-10), (I'-11), (I'-12), and (I'-13), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

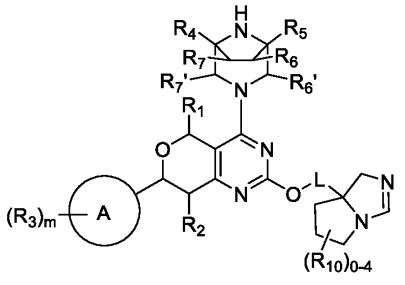
 (I'-3),  (I'-4),

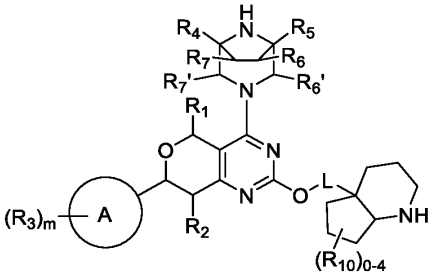
 (I'-5),  (I'-6),

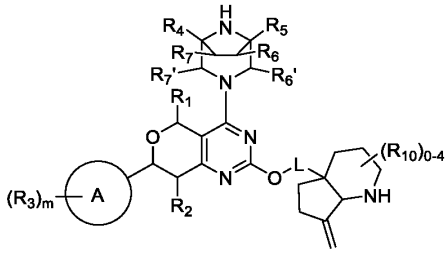

(I'-7),


(I'-8),

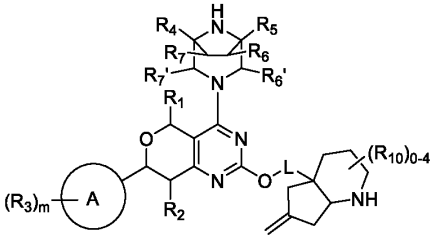

(I'-9),


(I'-10),


(I'-11),

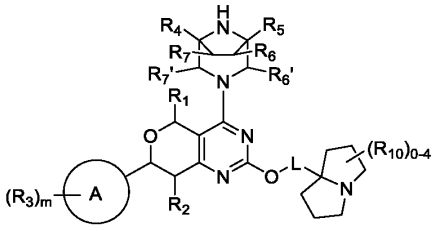
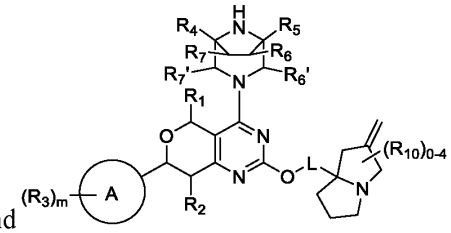

(I'-12)

and

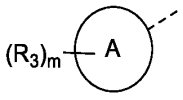
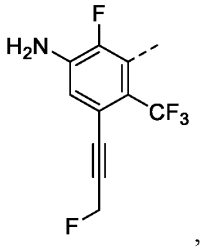

(I'-13).

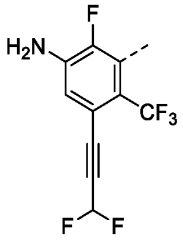
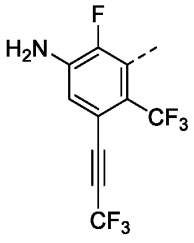
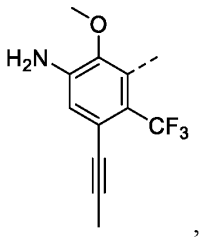
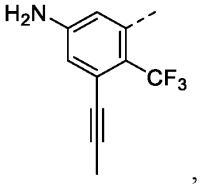
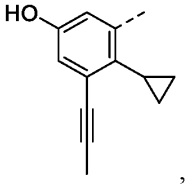
16. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 7-13 and 15, wherein R_4, R_5, R_6, R_7, $R_{6'}$ and $R_{7'}$ are selected from H.

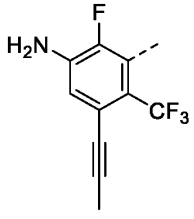
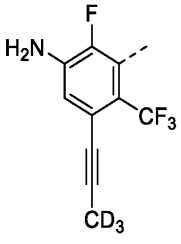
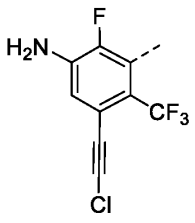
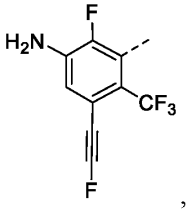
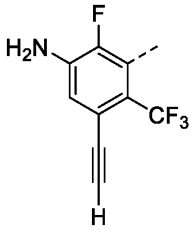
17. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 14, selected from a compound of Formula (I'-14) and (I'-15), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,


(I'-14) and 
(I'-15).

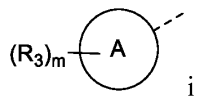
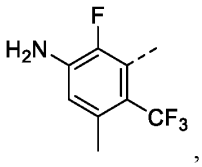
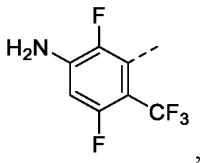
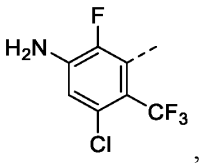
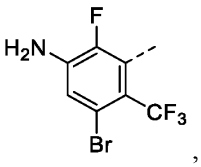
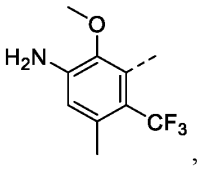
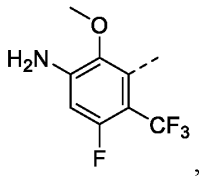
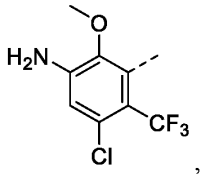
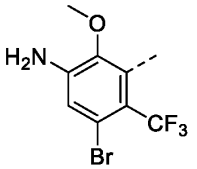
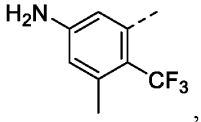
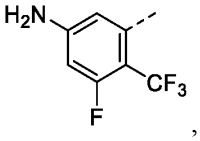
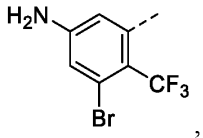
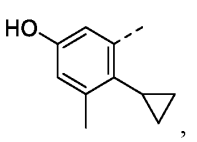
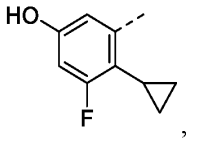
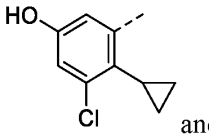
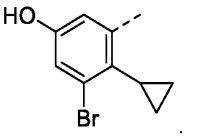
18. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-5 and 7-17, wherein Ring A is selected from phenyl, and is substituted with at least one R_3, and each R_3 is independently selected from F, OH, NH_2, CF_3, OCH_3, $-C{\equiv}CCH_3$, $-C{\equiv}CCH_2F$, $-C{\equiv}CCHF_2$, $-C{\equiv}CCF_3$, $-C{\equiv}CCD_3$, $-C{\equiv}CH$, $-C{\equiv}CCl$, $-C{\equiv}CF$ and cyclopropyl.

19. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-5 and 7-17, wherein  is selected from ,

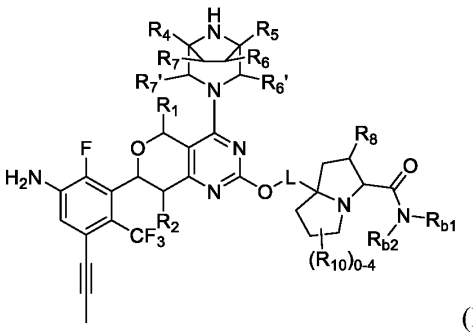
, , , , ,

, , , , and .

20. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any

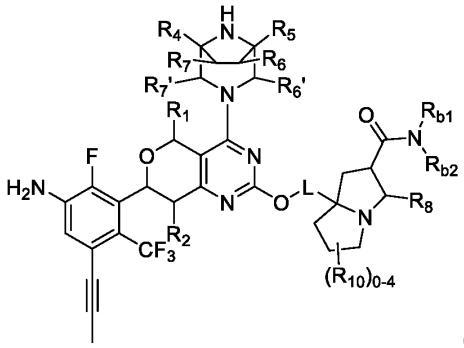
one of claims 1-5 and 7-17, wherein  is selected from , , , , , , , , , , , , , , , and .

21. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-1'-i) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



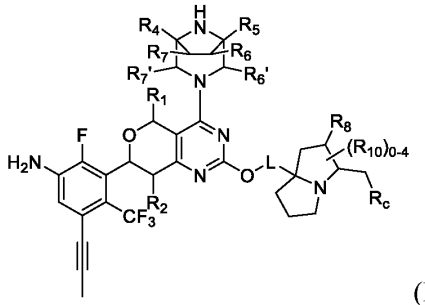
(I'-1'-i).

22. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-1'-ii) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



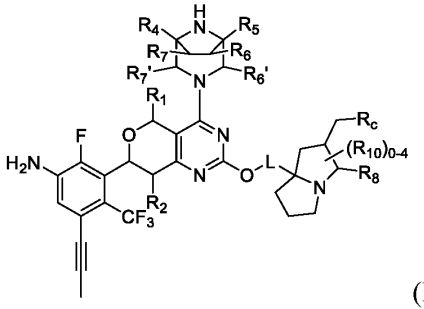
(I'-1'-ii).

23. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-2'-i) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



(I'-2'-i).

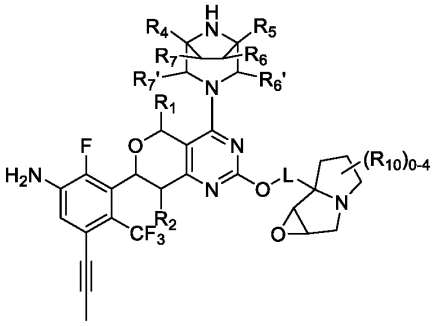
24. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-2'-ii) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



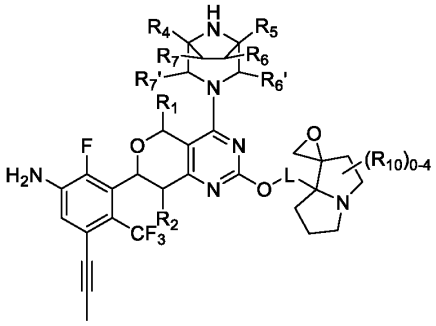
(I'-2'-ii).

25. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-3'), (I'-4'), (I'-5'), (I'-6'), (I'-7'), (I'-8'), (I'-9'), (I'-10'), (I'-11'), (I'-12'), and (I'-13'), or a stereoisomer thereof, or a pharmaceutically

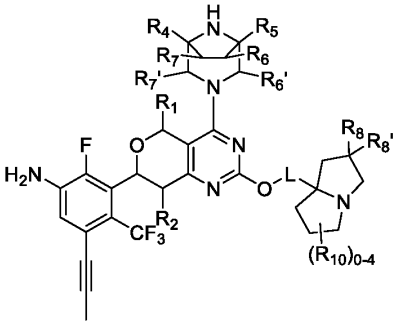
acceptable salt thereof,



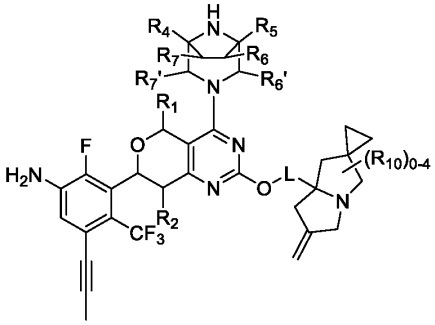
(I'-3'),



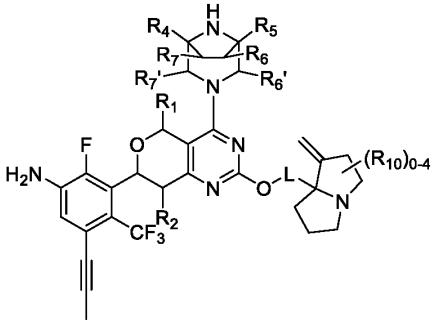
(I'-4'),



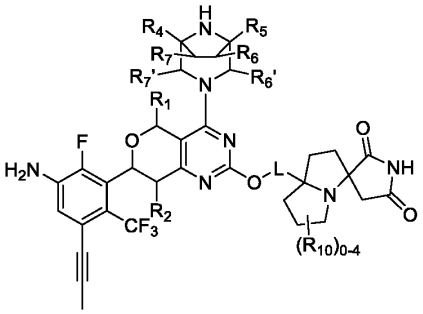
(I'-5'),



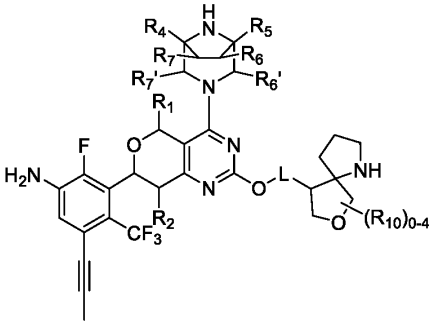
(I'-6'),



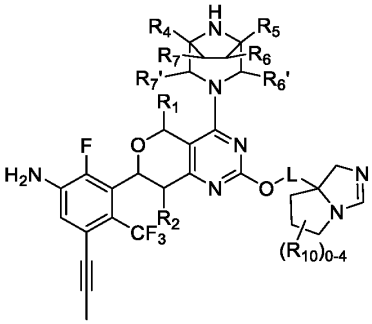
(I'-7'),



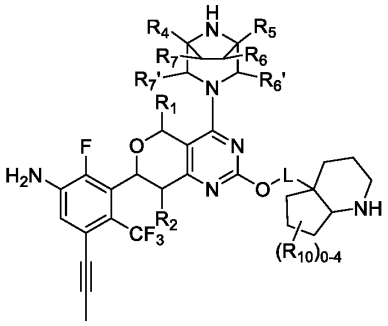
(I'-8'),



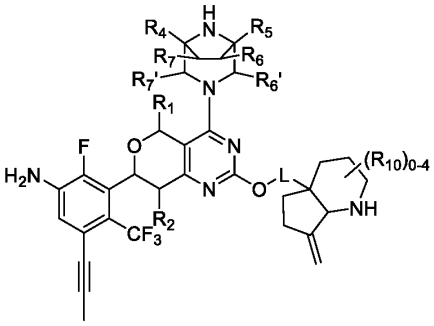
(I'-9'),



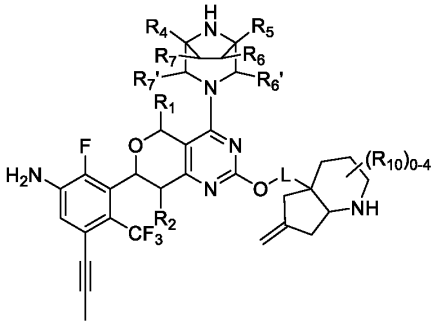
(I'-10'),



(I'-11'),



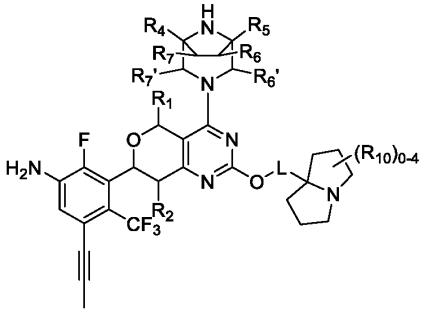
(I'-12'), or



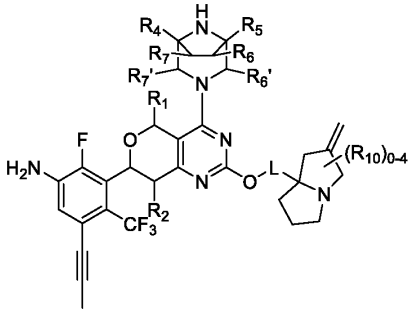
(I'-13').

26. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 25, wherein R_4, R_5, R_6, R_7, $R_{6'}$, and $R_{7'}$ are selected from H.

27. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 19, selected from a compound of Formula (I'-14') and (I'-15'), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



(I'-14') and



(I'-15').

28. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein L is selected from $-C(R_{L1}R_{L2})-$, and R_{L1} and R_{L2} are each independently selected from H and D.

29. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein L is selected from -C($R_{L1}R_{L2}$)-, and R_{L1} and R_{L2} are each selected from H.

30. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein L is selected from -C($R_{L1}R_{L2}$)-, and at least one of R_{L1} and R_{L2} is selected from C_{1-3} alkyl.

31. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-30, wherein R_1 and R_2 are selected from H.

32. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, selected from Table 5 or Table 5a.

33. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 32, selected from Table 6 and Table 6a.

34. Use of the compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-33, in the preparation of a medicament for the treatment of a disease or disorder associated with a KRAS mutation.

35. The compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-33, for use in treating a disease or disorder associated with a KRAS mutation.

36. A method of treating a disease or disorder associated with a KRAS mutation, comprising 2dministering to a subject in need thereof the compound or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1-33.

37. The use of claim 34, the compound for use of claim 35, or the method of claim 36, wherein the KRAS mutation is a KRAS G12D mutation.